

FLOYD ELWOOD KEENE
1881—1938

American Journal of Obstetrics and Gynecology

VOL. 37 JANUARY, 1939 NO. 1

IN MEMORIAM

FLOYD ELWOOD KEENE
1881-1938

FLOYD ELWOOD KEENE, member of the Advisory Editorial Board, was born Oct. 9, 1881, in Kewanee, Illinois. His youth was spent in Peoria, Illinois, where he received his preliminary education. Having graduated from the High School there, he entered the University of Pennsylvania Medical School and graduated in 1904. From his early medical school days he showed a keen interest and appreciation of medical sciences and applied himself to these most diligently throughout his academic career. His acute mind soon established him as one of the outstanding and scholastically brilliant members of his class.

Upon completion of his undergraduate career, and because of his unusual ability, he was selected as an interne for the University Hospital, which interneship he completed in 1906. By this time he had made many friends and admirers among his instructors, chiefs, the older men of the faculty, and the profession, who urged him to undertake postgraduate study, which advanced instruction he obtained in Berlin and Vienna, during 1907 and 1908.

His immediate association with the then eminent Goodell Professor of Gynecology, Dr. John G. Clark, upon his return, started his rapid rise in this specialty. Dr. Keene for many years was Dr. Clark's first assistant as well as his personal and much admired friend. He held the Chair of Assistant Professor of Gynecology at the University of Pennsylvania from 1922 until 1927. During his assistant professorship he soon became, under Dr. Clark's able supervision, a skillful operator and brilliant author. He assumed a deep interest in the study and early recognition of cancer and its treatment and in a large measure was responsible for the remarkable end-results obtained in this clinic. He soon became an authority on the use of radium in the treatment of both benign and malignant uterine lesions. As the technique of treatment changed from time to time, he was instrumental in bringing about what today is the well-recognized method of dealing with malignancy.

At Dr. Clark's untimely death, Dr. Keene succeeded him as Goodell Professor of Gynecology, in 1927, which Chair he held until his death.

During his medical life in Philadelphia, he made many sincere friends throughout the country, among the older as well as the younger members of the profession. He endeared himself to his patients by his kindness and sympathy, often sacrificing his own personal health to minister to the sufferings of others.

Dr. Keene was a member of the American Medical Association; American College of Surgeons; American Gynecological Society; Surgical Research Society; College of Physicians of Philadelphia; Obstetrical Society of Philadelphia; Philadelphia Academy of Surgery; Philadelphia Pathological Society, and Phi Delta Theta, Alpha Omega Alpha (Hon.), and Phi Alpha Sigma (Medical) Fraternities. In some of the many societies of which he was a member, he held high rank, being Secretary for five years and subsequently President of the American Gynecological Society from 1933 to 1934; President of the Philadelphia Obstetrical Society from 1931 to 1932.

Dr. Keene published many noteworthy articles relative to his specialty. An alert observer, quick to accept sound advances, he became one of the foremost gynecologists of his day.

He served overseas with distinction, as a member of Base Hospital No. 20 U.S.A. He married Marthe Bussiere, of Pay de Dome, France, after the termination of the World War, and returned to his work in Philadelphia.

He died at his home in Wynnewood, Pennsylvania, following a brief illness, on November 15, 1938. He is survived by his widow, a daughter, Jeanette, and a son, John Clark Keene.

Dr. Keene's untimely death came as a great shock to his many friends. His loss to the profession cannot be estimated, but he will always remain as a guiding star because of his professional and personal honesty, his ability and sincerity in his efforts to advance the sound principles of medicine.

Norris W. Vaux.

Original Communications

THE INCIDENCE OF ANOVULATORY MENSTRUATION AMONG PATIENTS OF LOW FERTILITY

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FOR the solution of any problem of infertility, we attempt to examine the integrity of what we consider the six essential factors of fertility; namely, ovulation, spermatozation, insemination, conjugation, migration, and nidation. The proper fulfillment of all these functions is necessary for a normal human conception. Only two of them are easily examined, spermatozation and insemination. The quality of the other functions must be deduced from indirect evidence: migration (of both spermatozoa and zygote) by its possibility because of the patency of the cervix, uterus and tubes; conjugation, by the postponement of otherwise justifiably expected menstruation; normal nidation, by the further prolongation of amenorrhea and the absence of signs of ectopic gestation; and finally, ovulation, with which we are here concerned, by equally indirect methods as yet. The time seems fast approaching when we may have a direct and prompt index of ovulation, since Burr, Hill and Allen[1] have demonstrated ovulation in the rabbit by its electrical effect. As recently as June, 1937, Rock, Reboul and Wiggers,[2] adopting Burr's technique, obtained a similar electrical reaction in one woman, and in another woman such a sign was obtained by Burr[3] and his co-workers. Until this or some other method is perfected, we must depend in most cases on the older indirect means of deducing ovulation from demonstrable evidence of corpus luteum activity. Study of ovarian behavior in subprimate mammals justifies us in assuming such activity to occur only following normal ovulation. (The quality of the ovum, except as vouchsafed by this phenomenon, is beyond our examination.) The evidence of corpus luteum function is found in the endometrium, where progestin-specific changes have been described by many in this country as well as abroad. (Corner and Allen,[4] 1929; Bartelmez,[5] 1933; Rock and Bartlett,[6] 1937.)

Menstruation was formerly considered presumtive evidence of ovulation, but now we demand menstruation from a secretory mucosa as an indication. For clinical purposes we may demand even more than this, and consider effective ovulation to have taken place only if a corpus luteum effect is found to persist for a minimal period. Arbitrarily, we select ten days for this interval between the beginning of corpus luteum or progestin effect in the endometrium and menstruation.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

MATERIAL AND RESULTS

This investigation of the frequency of anovulatory menstruation is based upon a study of biopsy specimens of the uterine endometrium obtained by the small suction curette from patients complaining of sterility. The advantages and limitations of the suction curette for study of the endometrium have been described by Klingler and Burch[7] (1932), Rock[8] (1934), Novak[9] (1935), Kurzrok[10] (1937), Rock and Bartlett[6] (1937), and others. It is emphasized that these biopsies may be repeated frequently, without anesthesia, as an office procedure, and are therefore adaptable to investigation of successive cycles or to study at intervals throughout a single cycle.

This report considers 392 patients upon whom biopsies were performed. In these cases the preceding and succeeding menstrual dates as well as the menstrual history of the patients are known. Repeated biopsies were obtained from a large proportion of them.

Thirty-six patients of this group showed evidence of anovulatory menstrual flow; that is, bleeding of normal duration from a nonsecretory endometrium at an interval of not less than three weeks from the previous menstrual flow, and not more than ten days after the biopsy was taken. All of these 36 patients showing evidence of anovulatory menstruation were within the childbearing age. Eighty-eight per cent of them were between 20 and 34 years of age and the remainder, between 35 and 39. The biopsies were taken as follows:

38 per cent on the day of flow;
35 per cent on the first or second day previous to the flow;
18 per cent on the third to seventh days previous to the flow;
9 per cent on the eighth to tenth days previous to the flow.

Only five biopsies are counted in this series, then, which were taken more than a week preceding the menstrual flow, and these were taken on the eighth, ninth, and tenth days. Biopsies taken more than ten days before the succeeding flow we believe should not be considered, because then the formation and regression of a functioning corpus luteum becomes possible, though such a sequence is probably not normal in less than twelve days. These findings indicate an incidence of 9.1 per cent of sterile women who show evidence of anovulatory menstruation.

Of these 36 patients, 18, or 4.6 per cent of all sterility patients in this series, showed evidence of anovulatory menstruation on more than one biopsy:

10 patients had 2 anovulatory periods
2 patients had 3 anovulatory periods
2 patients had 4 anovulatory periods
1 patient had 6 anovulatory periods
2 patients had 7 anovulatory periods
1 patient had 8 anovulatory periods

Eight of the patients, or 22 per cent, showing anovulation also showed bleeding from a secretory endometrium, definite evidence of ovulation, at a subsequent biopsy. Cases illustrating this combination of anovulatory with true menstruation are described below.

Since the clinical diagnosis of anovulatory menstruation would be of great significance in dealing with sterility patients, it is important to analyze the menstrual habits of this group and also of sterility patients in general.

TABLE I. RELATIVE FREQUENCY OF MENSTRUAL IRREGULARITIES AMONG STERILITY PATIENTS AND THOSE SHOWING ANOVULATION

TYPE OF MENSTRUAL ABNORMALITY	36 PATIENTS SHOWING EVIDENCE OF ANOVULATION	356 STERILITY PATIENTS
Oligomenorrhea	14 or 38.8%	35 or 9.8%
Amenorrhea	10 or 27.8%	11 or 3.1%
Irregular catamenia	8 or 22.2%	26 or 7.3%
Metrorrhagia	4 or 11.1%	41 or 11.5%
Polymenorrhea	3 or 8.3%	27 or 7.5%

Table I records the relative incidence of various types of menstrual abnormalities among the infertile patients who had at least one anovulatory period and among those in whom none such was discovered.

These figures indicate that a history of periods of amenorrhea is nine times as frequent in sterility patients showing anovulatory menstruation as in others; oligomenorrhea, four times as frequent; and irregular catamenia, three times as frequent; whereas a history of metrorrhagia and of polymenorrhea appears in both groups with about the same frequency.

While these results do not indicate that anovulatory menstruation can be diagnosed from the sterility patient's menstrual history, they are at least suggestive. We believe that with an infertile patient a history of periods of temporary amenorrhea, of oligomenorrhea, or of irregular catamenia should arouse suspicion of anovulatory menstruation and should indicate repeated endometrial biopsy studies through several menstrual cycles.

In addition to the group of 36 patients considered to have had an anovulatory period, there were 11 patients who bled from a nonsecretory endometrium but were not included in our series because the flow occurred less than three weeks after the preceding flow. Such flow in these patients is, probably, anovulatory, but we think does not merit the diagnosis of menstruation, because of the short interval between periods. Seven of these entered with a complaint of metrorrhagia, two complained of oligomenorrhea, one of polymenorrhea, and one of irregular catamenia. One of these patients, at a subsequent biopsy, showed evidence of ovulation.

Biopsies on another group of 15 patients, who are not included in our series because the dates of the preceding and following periods of flow were not definitely established, showed bleeding from a nonsecretory endometrium. In this group, twelve complained of metrorrhagia. The complaint and the findings on examination are both characteristic of dysfunctional uterine hemorrhage.

Seventy-seven biopsies were performed on 54 patients complaining of amenorrhea. Of these 54 patients, only eight showed secretory endometrium, while the remaining specimens were proliferative or hypoplastic. The subsequent history of 3 of the 8 patients is unknown. Of the other 5, all flowed in a few days. It is not to be assumed that biopsy precipitated a flow which would not otherwise have occurred, since in over 400 biopsies showing secretory endometrium only 4 did not flow in sixteen days, and two of these flowed in twenty days. We cannot explain this delay in menstruation except by postulating a short pregnancy, or by assuming the most unlikely phenomenon of a persisting corpus luteum spurium. It appears, therefore, that practically all patients, even those with a history of amenorrhea, once they do ovulate, will flow after an interval of not more than sixteen days, unless conception occurs. When the infertile cycle is lengthened, we believe it is due to a prolongation of the preovulative phase and not to the prolongation of the secretory phase, by persisting progesterone effect; for in the absence of pregnancy we find no evidence of what has been commonly referred to as a "persisting corpus luteum."

CASES OF REGULAR ANOVULATORY MENSTRUATION

Occasionally one finds a patient in whom the periodicity and amount of flow is such as to justify her belief that she is menstruating normally, but biopsy proves her flow to be anovulatory. The records of 4 such patients follow:

CASE 1.—The case of Mrs. B. (121-239) was reported by Rock and Bartlett.[6] This patient flowed four times with fair regularity after being amenorrheic for over a year. The first three bleedings were shown by biopsy to have occurred from proliferative endometrium. The fourth was not preceded by biopsy.

CASE 2.—Mrs. D. (140-204), 22-year-old nulliparous Italian housewife. Her periods began at 15 years of age, the interval was at first regular from thirty to thirty-two days and the flow lasted eight days. Subsequently, the flow became irregular, and was reduced to four days' duration. At one time she was temporarily

amenorrheic for three months. Fig. 1 demonstrates that in two series of visits to the clinic this patient showed 12 menstrual periods occurring with fair regularity. Seven of them were preceded by biopsies showing hypoplastic or proliferative endometrium, and 5 intercurrent periods of flow occurred without preceding biopsy, showing that the catamenias were not precipitated by this procedure. This patient flowed for over a year with only slight irregularity but was never found to ovulate.

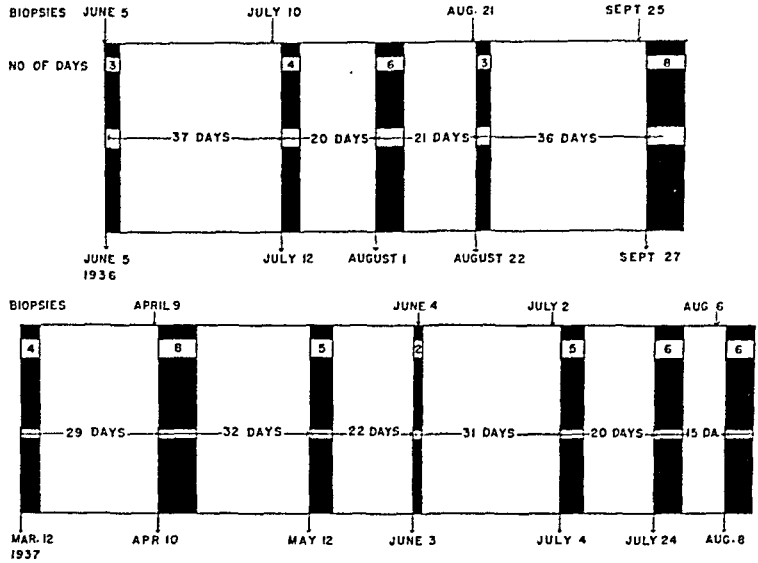


Fig. 1.—Anovulatory menstruation. Mrs. M. D. (140-204), aged 22 years. No labors. All biopsies showed proliferating endometrium.

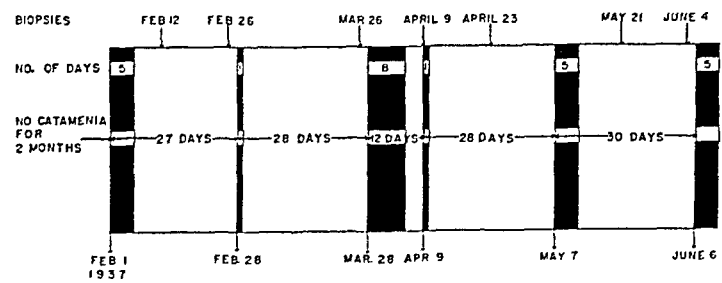


Fig. 2.—Anovulatory menstruation. Mrs. E. S. (82-28), aged 31 years. Labors none, miscarriages 4, irregular catamenia. All biopsies showed proliferating endometrium.

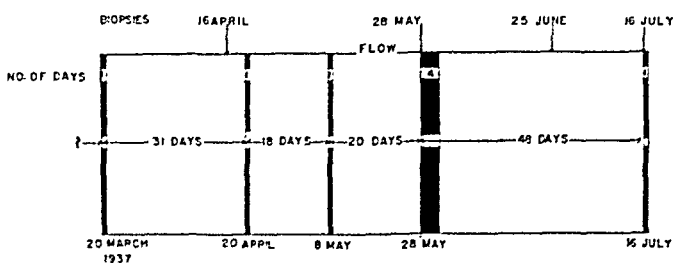


Fig. 3.—Anovulatory menstruation. Mrs. D. (146-141), aged 28 years. Labors none. Irregular catamenia. All biopsies showed proliferating endometrium.

Case 3.—Mrs. E. S. (82-28), a 31-year-old white housewife, with a history of four so-called miscarriages. Her periods began at 11 years of age, occurred at first every thirty days and then more irregularly. The flow usually lasted for four days. Fig. 2 shows the incidence of 6 periods of flow during four months, occurring with one exception at acceptably regular intervals. All biopsies showed proliferating endometrium in such time relation to succeeding flow as to rule out ovulation.

CASE 4.—Mrs. D. (146-141), a 28-year-old nulliparous, white housewife. Her periods began at 13 years of age and were regular, occurring every twenty-eight days, until four years before coming to the clinic. She usually flowed three or four days. Fig. 3 is a graph of 5 periods of scant flow in four months, three of which were preceded by biopsies showing proliferating endometrium.

CASES ILLUSTRATING BOTH ANOVULATORY AND OVULATORY MENSTRUATION

Eight of the 36 anovulatory patients were found by repeated biopsies also to flow after ovulation.

CASE 1.—Miss K. (140-100), who complained of polymenorrhea and dysmenorrhea, showed evidence of bleeding from both secretory and nonsecretory endometrium in 6 biopsies obtained at irregular intervals during six months:

DIAGNOSIS OF BIOPSY	DAY OF FLOW AFTER BIOPSY	CYCLE
1. 17-day	10th	ovulatory
2. Proliferative	7th	anovulatory
3. 18-day	6th	ovulatory
4. Proliferative	5th	anovulatory
5. 22-day	6th	ovulatory
6. 26-day	0	ovulatory

CASE 2.—Mrs. G. (131-356), a 23-year-old Italian housewife. Her periods began at 13 years and had been irregular with an interval usually longer than thirty days. She habitually flowed four days. In 1935 she flowed 5 times at fairly regular intervals of twenty-two to twenty-seven days, two of these catamenias being preceded by biopsies showing proliferative endometrium with dysplasia. These were followed by 5 months of amenorrhea during which two biopsies showed proliferating endometrium with dysplasia and one showed hypoplasia. Then the patient began to flow again at regular twenty-eight- to thirty-day intervals. Just before the fourth of these periods a biopsy showed typical secretory endometrium as did three more biopsies taken before succeeding periods. Apparently this patient, after an anovulatory interval of ten months, during part of which she was amenorrheic as well, suddenly commenced to ovulate again.

CASE 3.—Mrs. F. (137-278), who complained of periods of amenorrhea, showed evidence of anovulation and later proved she ovulated, once by biopsy and after that by becoming pregnant. The first biopsy was taken on the day she commenced to flow, after more than two months of amenorrhea, and showed late proliferative endometrium. Again she flowed two days after a biopsy showing late proliferative endometrium and twenty-nine days from the previous flow. Before the next biopsy was taken the patient had ovulated, for the endometrium obtained was characteristic of the fifth day of progestin influence and the menstrual flow followed in six days. Before the next catamenia the patient became pregnant.

DISCUSSION

The normal menstrual cycle of adult fertile human females is manifested in the uterine endometrium by a series of progressive changes culminating in the menstrual flow. These changes fall into two phases which correspond with ovarian endocrine activity: first, the proliferative stage under the stimulus of the estrogenic substances of the ripening follicle; second, the secretory stage characterized by glandular alterations and possibly secretion, and by stromal and vascular mutation under the stimulus of both the estrogenic and progestational principles

of the corpus luteum. In such a cycle, then, bleeding occurs from an endometrium built up under the stimulus of follicular hormones and subsequently modified by the hormones of the corpus luteum.

During the past decade, evidence has been accumulating from many sources that bleeding of such a character and duration as to be clinically indistinguishable from normal menstruation may occur from a non-secretory endometrium. Furthermore, the process of tissue destruction which eventuates in this form of uterine bleeding is not dissimilar to that which causes the shedding or deciduation of the normal predecidua.[6] Whatever the factors are which normally regulate the onset of the menstrual flow, it appears that the presence of the corpus luteum and with it the corresponding secretory or progestational transformation of the endometrium is not essential. Menstruation without preceding ovulation is probably a frequent occurrence at puberty, at the menopause, and in the post-partum period,[11] and apparently not infrequent among sterility patients during the childbearing age.

The first suggestion of anovulatory menstruation came from Heape[12] (1894; 1897) even before the time of ovulation was known at all. Heape collected menstruating uteri of *Semnopithecus* and *Macacus rhesus* monkeys and observed that very few of them were accompanied by ovaries which contained corpora lutea. Van Herwerden[13] (1905) reported observations on 87 Java *Macacques* among which two types of menstruating uteri were found: one with a narrow mucosa, resting glands and poorly developed vessels with which no corpus luteum was associated and a second type, with swollen mucosa, secreting glands and thick-walled vessels associated with a corpus luteum. This author postulated a breeding season during which menstruation was preceded by ovulation and a resting season when cyclical menstruation continued in the absence of ovulation.

The normal occurrence of anovulatory menstrual cycles in monkeys out of breeding season was firmly established by the work of several investigators in this country many years later. Corner[14] (1927), over a five-year period, found by repeated laparotomies and autopsies upon young mature female *Macacus rhesus* monkeys that menstruation occurred frequently when no corpus luteum could be discovered. However, he did conclude that when ovulation occurred in the monkey, the following menstruation seemed to come at a regular interval, about twelve to fourteen days. He described two types of bleeding endometrium, one showing proliferation only and the other progestational changes. Corner also cites isolated cases, including one observed by himself, of young women known to have had recent cyclic menstruation who were autopsied after death due to other causes and in whom no evidence of recent corpus luteum formation was found.

At this time, Allen[15] (1927) observed by correlating the number of regressing corpora lutea present with the preceding instances of menstruation in five monkeys, that ovulation occurred in less than 50 per cent of the cycles. Allen also found that menstruation occurred upon

the cessation of injections of lipoid extracts of ovarian tissue into spayed animals after a certain degree of growth had been induced by the injected hormone.

The overwhelming evidence of Hartman[16] (1932) definitely established anovulatory menstruation in the *Macacus rhesus*. He observed by numerous methods several hundred proved cases of menstruation without preceding ovulation and showed that in the monkey, ovulatory and nonovulatory cycles were followed by approximately the same amount of bleeding.

The problem of anovulatory menstruation in the human female is a much more difficult one to investigate and conclusions drawn from comparisons with the other primates are not easy to evaluate. Novak[17] in 1930 raised the question as to whether certain pathologic forms of hemorrhage in the human being which may still retain a certain periodicity are not to be looked upon as analogues of menstruation without ovulation in the monkey. These instances of bleeding when ovulation does not occur, and in which there is almost always a characteristic hyperplastic nonsecretory type of endometrium, may be, he thought, instances of an occurrence which may not be infrequent. Novak proposed that dysfunctional uterine bleeding, seen so characteristically at puberty and the menopause, is to be considered as reversion to the follicular type of sex cycle seen in most of the lower animals, including some monkeys.

By 1934 Novak[18] was ready to assert beyond dispute that anovulatory menstruation occurs in some women. He says: "Functional menorrhagia, at times not very excessive, is characteristically associated with an anovulatory mechanism and undoubtedly it occurs in some cases in which the menstrual flow is within normal limits." Novak believes that the proportion of anovulatory cycles in normally menstruating women is very small but that in unexplainable cases of sterility it may be very high.

Experimental hormone injections by various workers have contributed materially to this problem. Following the preceding demonstrations of Clauberg[20] and Kaufmann,[21] those of Werner and Collier[22] (1933) are very significant. In four women showing endometrial atrophy following bilateral oophorectomy, large doses of theelin resulted in hyperplasia of the endometrium and repeated flow from the nonsecretory endometrium. All four patients bled during the injections and three, after the injections were stopped. Their bleeding was qualitatively indistinguishable from menstruation in normal women, though there was quantitatively less loss of tissue. The patients are also said to have experienced the symptomatology of menstruation. In these cases the absence of corpus luteum effect cannot be doubted. One of us[8] obtained similar results with two intact women whose ovaries were quite inactive.

Bartelmez[5] (1933) examined with great care a number of menstruating uteri obtained at operation. He found that various portions of the uterus respond differently to hormonal stimuli, a fact which we believe may account for many of the discrepancies found in reports upon endometrial specimens. As pointed out by Rock and Bartlett[6] (1937),

specimens taken from the mucosa high on the anterior or posterior wall of the fundus most consistently show the characteristic cytologic changes. Bartelmez concludes that the only invariable endometrial changes observed during menstruation are vascular. In his series he considers that he has one case with all the necessary data to prove anovulatory menstruation and four which suggest it.

Mazer and Ziserman[19] (1932) reported a series of 41 functionally sterile women subjected to premenstrual curettage among whom 24 showed a "non-nidatory" endometrium indicating defective luteinization or total absence of a corpus luteum. In our larger series of barren women so high a percentage was not found.

Anspach and Hoffman[23] in 1934 reported on 42 cases of apparently normal menstruation, 9 of which showed endometrium of the "interval," "hyperplastic," or "atrophic" variety, an incidence of over 20 per cent anovulatory menstruation, which again is a much higher percentage than was found in our series.

In contrast to these reports is that of the English investigator Shaw[24] (1934) who believes that it is probably very exceptional to find no corpora lutea in the ovaries of women who have menstruated regularly. He examined 30 specimens between the fourteenth and twenty-eighth days of the cycle and found them all to show secretory endometrium. He concludes that cyclical uterine bleeding is accompanied by ovulation and that bleeding independent of ovulation should be looked upon as so definitely pathologic, as not to be dignified with the term "menstruation."

Another English observer, Jeffcoate[25] (1935), in a series of 63 specimens from uteri obtained at operation between the twenty-first and the twenty-eighth day after the last period, in infertile subjects with regular cycles, found 16 which showed no evidence of luteal influence. This indicates an incidence, again, of 25 per cent anovulatory menstruation among sterility patients, a figure far in excess of our findings. In Jeffcoate's specimens, of course, the actual date of the following menstruation was not obtainable: a significant criticism which applies to all the cases in which specimens were obtained from extirpated uteri. Jeffcoate also examined by curettage the endometrium of 21 women who were supposedly in the premenstrual or menstrual period and found that 10 (or 48 per cent!) showed no sign of secretory activity. Because of the known variability of the preovulatory phase, this finding alone cannot be considered evidence of anovulatory menstruation.

In 1935, Bland, First and Goldstein[26] in this country reported the following results upon premenstrual curettage of 50 regularly menstruating sterile women: Premenstrual endometrium, 23; interval endometrium, 15; hypertrophic endometrium, 9; atrophic endometrium, 3. In other words, less than 50 per cent of this series showed endometrial evidence of corpus luteum activity. They state that in the cases of interval, hyperplastic or atrophic endometrium, "should fertilization occur the endometrium is not prepared to retain the embryo, and

abortion inevitably results." We do not believe that in these cases fertilization is even possible, for without the premenstrual changes in the endometrium, the release of a fertilizable ovum must be considered most unlikely.

The most recent series of cases reported is that of Mazer, Israel and Kacher.[27] They found that 19 out of 65 selected functionally sterile women showed no evidence of the secretory phase in uterine curettings taken one to six days before the expected menstrual flow, from which they conclude that "cyclic uterine bleeding, clinically indistinguishable from normal menstruation, from an endometrium totally lacking the usual secretory changes, occurs in 30 per cent of sterile women who present no abnormality." These authors prefer the term "pseudomenstruation" to "anovulatory menstruation" when the diagnosis is based on endometrial findings alone since they believe that anovulation cannot be proved without concomitant study of the ovaries. We, however, have assumed that the presence or absence of secretory endometrium in the suction biopsy indicates the presence or absence of a functioning corpus luteum. Again as with the figures of Mazer and Ziserman,[19] of Anspach and Hoffman,[23] of Jeffcoate,[25] and of Bland, First and Goldstein,[26] we fail to find so high a percentage of cases of anovulatory menstruation.

SUMMARY AND CONCLUSIONS

1. Endometrial biopsies obtained by the small suction curette provide a useful and adequate means for determining the occurrence or failure of ovulation.

2. The diagnosis, anovulatory menstruation, should be distinguished from that of intermittent and irregular bleeding, better termed metrorrhagia.

3. In a series of 392 women complaining of sterility, about whom adequate information was available, 9.1 per cent showed evidence of at least occasional anovulatory menstruation.

4. About 4 per cent of sterility patients may be considered habitually anovulatory, because, for at least several months, they exhibit regular menstrual flow which is clinically indistinguishable from normal menstruation, but which comes from a proliferating or a hypoplastic endometrium.

5. Patients who usually flow regularly from a normal secretory endometrium may occasionally flow from a persisting proliferative endometrium.

6. Sterility patients with a history of menstrual irregularities, even though flowing normally at the time of examination, should arouse suspicion of anovulatory menstruation since such a failure of ovulation is three to nine times more frequent among these patients, than among those whose menstrual history is normal.

7. Anovulation and amenorrhea are commonly coexistent. Anovulation and regular or slightly irregular menstruation are occasionally co-

existent. Ovulation infrequently occurs in patients who are habitually amenorrheic.

8. A brief review of the literature on anovulatory menstruation is presented.

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THE DEGREE OF NORMAL MENSTRUAL IRREGULARITY*

An Analysis of 20,000 Calendar Records From 1,500 Individuals

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IT IS a traditional medical teaching that women usually exhibit a regularly spaced menstrual rhythm. That this belief still reflects accurately the opinions of many obstetric and gynecologic authorities is shown by their published statements. Representative lists of such textbook references have been given by Fluhmann (1934) and by Gunn and others (1937); it would be easy to extend these citations. Moreover, one is safe in asserting that it is the custom, both in better hospitals and private practices, to assume the normality of menstrual regularity as the basis of clinical questioning for case history purposes.

The commonest source of information from which judgments concerning menstrual periodicity have been derived is the hospital case record. As typical examples may be cited the extensive compilations by Sanes (1916) in this country, Nakagawa (1931) in Japan, Kennedy

*Contribution No. 245. Acknowledgment is due several persons who have supplied information to further the completion of this report. Drs. E. Allen, C. F. Fluhmann, J. L. King, L. J. Latz, J. P. Pratt, and M. C. Shelesnyak have cooperated by sending miscellaneous, supplementary data to clarify and extend their published accounts of group studies.

(1933) in Scotland, and Hajek (1933) in Czechoslovakia. Characteristic of this kind of inquiry is the conclusion of Nakagawa that 97 per cent of this group of 2,080 selected women menstruated regularly, or that of Kennedy who credits 75 per cent of 9,768 patients with having a regular twenty-eight-day cycle. The uncritical attitude customarily exhibited on these matters is well illustrated by Knaus (1934), who, bent on doing a bit of special pleading for his "safe period," explains away Kennedy's high (sic!) percentage of irregularly menstruating women on the basis of the group being drawn from gynecologic patients and not from a normal, healthy population. It is also Knaus who was irked by Fraenkel's well-known paradox concerning the irregularity of the menstruating woman ("Das einzig Regelmässige an der Regel ist ihre Unregelmässigkeit") into stating that he was "not prepared to settle this very important question in quite such an airy fashion without any foundation of fact"; whereupon he proceeded unquestioningly to accept, as the foundation stone of his theory, tabulations from routine hospital histories!

Historically fundamental to a popular belief in a regular twenty-eight-day cycle is the world-wide tradition of lunar influence. This superstition has been fostered through the influence of Arrhenius (1898) and has been credited by De Lee (1934) and others. However, Gunn, Jenkin and Gunn (1937), using reliable menstrual data, find no justification for associating the date or rhythm of menstruation with lunar phenomena; they are also able to show how Arrhenius reached his conclusions through the use of wholly unreliable data. In addition, it is now sufficiently established that an abetting factor that has done much to confuse the true picture of menstrual periodicity is the utter unreliability of woman's unaided memory in these matters. Her testimony may not even be consistent on different occasions of questioning (Sanes, 1916). Moreover, even if woman's memory concerning her own menstrual history were trustworthy, the mere method of approach by which menstrual histories are customarily obtained for clinical records would still load the scales against the truth: the questioner suggests by implication the "normal" reply expected; the patient senses that any other answer will mark her as atypical, and so reacts instinctively in a protective manner; the easiest way for her to avoid further discussion of an often embarrassing and seemingly inconsequential topic is to give the answer suggested, and especially so since "regularity" is entirely a relative measure that depends upon personal standards of interpretation.

For these reasons the analysis of accumulated hospital records is fruitless, while the numerous published articles dealing with menstrual periodicity, which have been based on these records, are without value. Only data taken from actual calendar records of women who are interested and responsible (or otherwise are adequately supervised) are acceptable for serious consideration. Fortunately there is a limited number of studies, published mostly within recent years, which make available the lengths of consecutive menstrual cycles as recorded by selected women over different periods of time. The general trust-

worthiness of these data has been reasonably safeguarded by various means and it is believed they are, on the whole, as accurate as may well be expected under such circumstances. It is the purpose of the present article to select and assemble these data, to subject them to statistical methods of analysis, and to reinterpret them both as individual studies and as a composite group. In this way it seems possible to bring to a conclusion certain fundamental inquiries regarding menstrual periodicity. This does not imply that the further collection of menstrual data is not badly needed. On the contrary, it merely signifies that the time has come to close certain of the simpler problems whose answers are sufficiently at hand and to direct future energies into resolving those other features of the menstrual function on which exact information is still lacking. For example, rather than to collect further quantities of short records, it will be far more profitable to seek out long-term menstrual histories and subject them to analysis. Richards (1935) and Hartman (1936; 1937) have already made a start in this direction, while the present writer will soon contribute also to this phase of the menstrual problem.

Some of the published menstrual data present the detailed records of the actual participants; other sets of data conceal this individual information and, instead, combine the cycles of all participants into one group. In a corresponding manner, the conclusions given sometimes represent generalizations drawn from individual records and averages, while in other instances the massed cycles of all individuals have been treated as though emanating from a mythical "average woman." On the whole, the former treatment is more exact and instructive, although certain valuable facts, as well, do come out of merged data. As a practical matter it has been necessary, in every instance but two, to accept the data as printed and to make the best of them in that form.

THE DISTRIBUTION FREQUENCY OF MENSTRUAL CYCLES

Some worth-while information can be gained by arranging the data to show the distribution frequency of all the cycle lengths encountered. In Table I this has been done for nine studies on adults and one on pubertal girls. All these subjects were white inhabitants of the north temperate zone; further details pertaining to the several sets of data are listed in Table III, but here it is only necessary to state that the participants were all supposedly healthy, or at least without conflicting pelvic disease. As may be seen, the modes for the several adult groups are divided evenly over 27, 28, and 29 days; the grand mode, both for adult women and for girls, is set at 28 days.* In the adults this value is clearly established, while for pubertal girls there is little supremacy of 28 days over 26, 27, and 29 days. Although the recorded cycle lengths

*In contrast to the facts embodied in Table I it is enlightening to compare the recent conclusions of Hajek (1933) who relied upon the verbal testimony of 1,480 women as recorded in case histories at the polyclinic at Prague. He credits 82 per cent as being "regular." Of the whole number 56.7 per cent reported a 28-day cycle, while only 0.6 per cent and 0.06 per cent claimed 27- and 29-day cycles, respectively. The neglect of 27 and 29 days in these histories shows how small is the reliance that can be placed on the details of histories given from memory.

TABLE I. DISTRIBUTION FREQUENCY, ACCORDING TO LENGTH, OF 5,322 MENSTRUAL CYCLES EXPERIENCED BY 485 ADULT WHITE WOMEN, AND 3,140 CYCLES EXPERIENCED BY 100 PUBERTAL GIRLS. THE MODAL VALUES ARE INDICATED BY ITALICS

SOURCE OF DATA	NO. OF SUBJECTS	NO. OF CYCLES	LENGTH OF CYCLES IN DAYS																					
			7-10	11-15	16-20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36-40	41-50	51-100	101-256
1. Issmer, 1889	12	120			2	2	1	1	5	9	14	17	*22*	19	13	6	3	3	-		3			
2. Latz and Reiner, 1935	102	1,113		1	4	1	8	22	45	101	127	152	*202*	119	87	80	62	31	25	16	25	4	1	
3. Latz and Reiner, 1937	100	1,336			4	5	18	46	84	133	175	*218*	209	158	114	75	36	22	14	4	11	7	2	1
4. King, 1926	17	523			1	1	11	16	43	60	66	*97*	76	50	37	23	11	6	6	7	5	6	1	
5. King, 1933	37	354			4	3	11	10	23	25	33	*51*	36	45	36	15	20	15	6	5	7	6	3	
6. Scipiades, 1935	47±	319						3	15	12	18	25	36	*49*	36	17	32	24	9	11	16	11	5	
7. Allen, 1933	44±	511			13	8	10	15	28	46	37	55	55	*61*	60	50	20	15	13	5	20			
8. Fluhmann, 1934	76	747		10	33	17	16	28	34	36	52	60	72	*73*	57	47	37	32	24	17	50	29	18	5
9. Pratt and others, 1929	50	299			1	4	8	22	33	33	43	37	*50*	20	16	19	5	3	3		2			
10. Engle and Shelesnyak, 1934	100	3,140	14	51	166	102	135	140	146	164	191	193	*202*	193	183	150	114	105	86	69	224	199	278	35
1-8. Totals, adults	485	5,322		11	62	41	83	163	310	455	565	712	*758*	594	456	332	226	151	100	65	139	63	30	6
10. Totals, pubertal girls	100	3,140	14	51	166	102	135	140	146	164	191	193	*202*	193	183	150	114	105	86	69	224	199	278	35

of the adult women run from 11 to over 100 days,* most of the entries lie between 25 and 31 days. The greater variability shown by pubertal girls, before the menstrual function has been smoothly established, is not unexpected.

It is instructive to compare some similar data on Japanese women as combined from studies by Obata (Ogino, 1934) on 959 students (number of cycles not given), by Ogino (1932; 1934) on 694 healthy multipara (883 cycles), and by a woman's journal (Fujin-Koron; Ogino, 1934) which collected 1,665 cycles (number of subjects not given). For this group two of the component curves have a 31-day mode while the remaining mode is at 32 days. The combined data show a mode of 31 days. The majority of entries are within the limits of 27 and 34 days.

Table I does not support the existence of favored subordinate types of cycle length (*e.g.*, 14-, 21-, 35-, 42-day), as have so long been described and even credited by recent authorities (*e.g.*, Novak, 1922).† It contrasts sharply with Kennedy's (1933) conclusions, drawn from the verbal testimony entered in 10,000 hospital records, in which these seven-day stages are strongly stressed. Yet in the combined Japanese data it is of interest to find that at weekly intervals of 21, 28, 36, and 42 days there are slight elevations which disturb the otherwise even distribution. This is chiefly caused by corresponding irregularities in Ogino's curve on multipara. Such occurrences at regular weekly intervals could not appear fortuitously; either they are real features of the menstrual phenomenon in these women or they are due to bias or error on the part of those furnishing the data. The fact that the curve for white women, known to be carefully collected, shows no similar tendencies and that the other two component Japanese curves largely lack this feature make one suspicious that such rhythmic disturbances in this instance are without real significance. They could easily result from the inclusion of records which tend to approximate round numbers in terms of the nearest week. An inquiry conducted on 6,000 school girls by the London Association of the Medical Women's Federation (1930) shows the predilection for whole weeks resulting from oral testimony. Similar tendencies appear in hospital records, as is shown by the figures of Nakagawa (1930), Hajek (1933) and Kennedy (1933).

Another way of handling the distribution frequency is to use the mean or modal cycle length characteristic of each person involved. This has the advantage of showing the distribution according to individual performance rather than as massed data in which individual peculiarities are lost. In many respects the modes would seem to be the more significant of the two. Practically, however, the data available for analysis are often too limited to show a reliable mode that can be taken as truly characteristic.

Of the several studies listed in Table I, those of Pratt and others (1929), Allen (1933), and Scipiades (1935) lack the information necessary for establishing individual modes. For the remaining sets of data, the group modes, expressing the greatest frequency of the individual modes, can be listed as follows: King (1933), 27 days; Latz and Reiner (1937), 27 days; Issmer (1889), 28 days; Latz and Reiner (1935), 28 days; Fluhmann (1934), 29 days; Engle and Shelesnyak (1934), 29 days. It is interesting that, except for the group of pubertal girls, these modes duplicate those for the mass distribution of cycles as shown in Table I.

*There are only a few scattering entries below 20 and above 50 days, except for 55 entries from Fluhmann's (1934) group of nurses. Perhaps Allen's (1933) data for nurses would also have been well represented in these extreme cycle lengths had the information not been lost (footnote ‡, Table IV). It is a question whether some of these long intervals should not be considered amenorrheal and hence be excluded from normal courses, even though Fluhmann tried to eliminate abnormal subjects (p. 22).

†Papanicolaou (1933) and Gunn (1937) have cited various writers who advocate the existence of menstrual types based on multiples of seven days. Papanicolaou, himself, holds for a rarer 21-day cycle, which is a fundamental mammalian type, and a commoner, longer cycle (usually 28 days) which includes a double uterine cycle.

TABLE II.* DISTRIBUTION FREQUENCY, ACCORDING TO AVERAGE LENGTH OF MENSTRUAL CYCLE, OF 1,165 ADULT WOMEN (14,512 CYCLES) AND 100 PUBERTAL GIRLS (3,140 CYCLES). THE MODAL VALUES ARE INDICATED BY ITALICS

SOURCE OF DATA	NO. OF SUBJECTS	NO. OF CYCLES	LENGTH OF AVERAGE CYCLE IN DAYS																		
			16-20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36-40	41-50	51-100
1. Issmer, 1889	12	120								2	*9*	1									
2. Latz and Reiner, 1935	102	1,113				1	3	5	15	*17*	*17*	13	8	11	9		2	1			
3. Latz and Reiner, 1937	100	1,336				1	8	7	13	*25*	15	14	9	5	2					1	
4. King, 1926	17	523						1	3	3	2	*5*	2						1		
5. King, 1933	37	354					2	3	2	5	4	*8*	5	2	1	2	2	1			
6. Gunn, et al., 1937	770	10,000±	2	4	8	26	57	94	112	*116*	100	74	54	38	24	17	13	6	15	7	3
7. Scipiades, 1935	51	319	1		1	2	1	3	6	2	10	*11*	1	2	4	1	2		2	1	1
8. Fluhmann, 1934	76	747	1	1	2	1	1	3	7	5	7	7	*11*	4	6	5		2	5	4	4
9. Engle and Shelesnyak, 1934	100	3,140				2	1	2	4	3	6	9	*10*	*10*	9	8	2	7	15	9	3
1-8. Totals, adults	1,165	14,512	4	5	11	31	72	116	158	*175*	164	133	90	62	46	25	19	10	23	13	8
9. Totals, pubertal girls	100	3,140				2	1	2	4	3	6	9	*10*	*10*	9	8	2	7	15	9	3

*The exact number of cycles collected is not given by these authors beyond the general statement that: "The investigation was planned to obtain one year's data from each individual." However, it is evident from the text that some subjects furnished more data than this (their Tables II and III). Since Gunn and his co-workers considered all average cycle lengths of, for example, 28.0 to 28.9 days as being 28 days, their distribution frequencies are not entirely comparable to those used by the present writer who has listed averages between 27.5 and 28.4 as 28 days. To make Gunn's distribution approximate the others in the present table, half of the individuals constituting each entry have been dropped back to the day previous.

TABLE III. GENERAL DATA CONCERNING MORE THAN 15,500 MENSTRUAL CYCLES FURNISHED BY 1,189 WOMEN AND GIRLS

SOURCE OF DATA	NATIONALITY	OCCUPATION	NO. IN GROUP	AGE RANGE AT START (YEARS)	MEAN AGE (YEARS)	TOTAL NO. OF CYCLES	RANGE IN NO. OF CYCLES REPORTED	MEAN NO. OF CYCLES PER PERSON	SHORTEST AND LONGEST CYCLE (DAYS)
1. Foster, 1889	American	Selected patients	56	----	----	330	5; 18	6.8	16; 46
2. Issmer, 1889	German	Housewives	12	19-39	26.8	120	10; 10	10.0	20; 40
3. Latz and Reiner, 1935	American, Canadian	Housewives	102	20-45	31.0	1,113*	6; 44	10.9	15; 51
4. Latz and Reiner, 1937	American, Canadian	Housewives	100	21-49	31.7	1,336	7; 49	13.4	19; 101
5. King, 1933	American	Industrial workers	21	17-35	23.3	161	4; 13	7.7	16; 57
6. Gunn, et al., 1935	British	Professions	479	13†-51	27.3†	6,000†	----	13.0†	----
7. King, 1926; 1933	American	College women	33	17‡-35	23.8	716	3; 104	21.7	18; 53
8. Scipiades, 1935	Hungarian	University students	50	18-34	24.5	339§	----	6.6	20; 91
9. Pratt, et al., 1929	American	Nurses and office workers	50	12-36	----¶	299	----	6.0	19; 36
10. Allen, 1933	American	Student nurses	110	----	----	1,291	----	11.7	13; 84
11. Fluhmann, 1934	American	Student nurses	76	18-27	20.4	747	3; 19	9.8	11; 144
12. Engle and Shelesnyak, 1934	Jewish-American	Orphanage inmates	100	11-15	13.1	3,140	20; 69	31.4	7; 256
1-11. Totals, etc. (adult groups)			1,089	12-51	26.1	12,452	3; 104	10.7	11; 144
12. Totals, etc (pubertal girls)			100	11-15	13.1	3,140	20; 69	31.4	7; 256

*Seven cycles have been omitted from the record of Subject 149 in the original report. These cycles are atypically long and there is an accompanying notation that the individual was suffering from an ulcer of the stomach during this period.

†Only six individuals were under 18 years of age. The average age, total number of cycles and mean number of cycles furnished by each person are approximations deduced from the incomplete data as furnished.

‡The record of one individual included 24 cycles starting from the time she was 13½ years old. After a break of eight years the record was resumed. These earlier cycles have been included in the computations, since, strangely enough, they are not inconsistent with her later rhythm.

§Although the total number of cycles is stated to be 386, a smaller number (339) is actually used in the detailed analysis given. There are some additional discrepancies and suppressions in the handling of these data so that no mathematical treatment can be perfectly consistent or quantitatively exact.

¶See p. 21, last paragraph.

The distribution according to the mean cycle length of individuals is presented in Table II. This information was obtainable from eight groups of adults and one group of pubertal girls. As with the distribution of modes, just discussed, this style of tabulation permits the menstrual tempo of individuals to show as entities. In five of eight groups where direct comparisons can be made with Table I there is a shifting of the group modal values; yet the decisiveness of the grand mode for the combined groups is changed but little. The grand mode of the means of all adults is 27 days, while the corresponding grand mode of the pubertal group is shared by 30 and 31 days. Again, any evidence for favored types, spaced at weekly intervals, is lacking and the distribution curve throughout approximates the even form customarily considered normal.

DETAILED ANALYSIS OF GROUP DATA

The distribution curves, shown in Tables I and II, theoretically might be produced either by closely spaced, individual records which are highly regular or by overlapping records of considerable individual variability. In order to ascertain which possibility is correct one must scrutinize individual records, accurately kept. Yet it is remarkable how few of these have been collected until recently. Scientific curiosity was quick to invade almost every aspect of human behavior, yet it long neglected this most obvious one. Menstrual regularity has been so thoroughly assumed that only a few persons have ever thought it worth while to gather reliable information through the medium of actual calendar records. All of the contributions of this sort which I have been able to discover are reviewed in the paragraphs which follow. In order to make the several studies more easily compared, some of their general data have been assembled as Table III. This tabulation, like those which follow it, has been prepared by working over the raw data of the original papers and adding, where possible, other desirable information obtained through correspondence with the authors. In this way the data have been corrected and altered in some instances, while in others they have been made more complete than the original publications show. Some apparent disagreements with the original publications are due to errors which exist in those communications but which have now been eliminated. The following notes supplement Table III by presenting certain information, mostly of a general nature, not amenable to tabulation.

The factual attack on the problem of menstrual regularity is not altogether new.

As long ago as 1889 Foster reported on 56 New York women, 20 of whom had at some time been pregnant, under his observation for various affections. Having included only those whose ailments were not accompanied by disordered menstruation, he obtained calendar records of 5 to 18 periods from each participant. The cycles ranged from 16 to 46 days in length. One patient reported perfect regularity throughout her period of observation, but the length of this span was not given. The cycles of the remainder showed a maximum variation of 1 to 18 days from a 28-day norm, although whether this departure was from the group mean or from an arbitrary 28-day standard is not now determinable. It is interesting to read the discussion which followed the presentation of this report; several clinicians maintained that such widespread irregularity must have been due to pathologic conditions. Even today, nearly fifty years later, similar comments are being made on similar occasions!

In the same year Issmer (1889) in his noteworthy contribution on the duration of pregnancy included the menstrual records of 12 Bavarian housewives for ten

months preceding pregnancy. The shortest cycle was 20 days and the longest 40 days, while no person was regular in the menstrual function. The maximal departures from individual means ranged from 2 to 12 days.

These two reports should have opened the eyes of physicians to the desirability of collecting additional information, but they were without appreciable effect and the time-honored faith in normal menstrual regularity continued to dominate clinical thought. Hence one must pass over an interval of some forty years before the next serious contribution appeared. This study was made by King (1926; 1933), but before considering her investigations in detail it may be simpler to continue with some other reports made on women drawn from the general population.

Somewhat comparable to Foster's original material was a heterogeneous group observed by Geist (1930). His brief report covers 200 women who kept records for one year. Most of these were patients, who, though not actually ill or suffering from pelvic disease, were under observation for various reasons. Those women who had previously declared their periods occurred on a specific day found themselves in error. "In most instances, however, there were variations . . . from five days before the accepted time to ten days after, and this variation occurred almost as frequently as would the so-called normal cycle." In a few individuals 28-day periods were experienced for nine of the twelve months and in some others there was extreme irregularity for six to seven months and then suddenly a return to a 28-day cycle for the rest of the year. No other details are given in this report, and, unfortunately, attempts to supplement these meager facts through correspondence have been unsuccessful; for these reasons it is not possible to include Geist's results in Table III or to consider them further for detailed analysis.

Two other sets of data drawn from the general population have recently been published by Latz and Reiner (1935; 1937). Included are 2,449 cycles which 202 women from various parts of the United States and Canada had recorded on calendars and sent these authors in the hope of establishing their ovulatory rhythm. Although unsupervised, it would seem that the purpose (contraception by the "natural method") for which the data were collected should have been a sufficient incentive to insure accuracy. Yet to a certain degree these records are selective and show a greater regularity than the average; especially do women who are so irregular that they feel they cannot use the method, fail to submit their records (private communication). In any event, the cycle lengths given range from 15 to 101 days, no record is regular, and the maximum departures from individual means vary from 1 day* to 53 days. In numerous instances notations of illness (including colds), fright, abortion, mental stress, physical strain, change of climate, etc., are recorded as accompanying unusually long or short cycles. If these cycles are removed as atypical, as Latz believes they should be (private communication), then the regularity increases appreciably. Latz and Reiner conclude that 90 per cent of women show a range of variation not exceeding eight days and that 80 per cent of all women menstruate regularly enough to make safe use of the Ogino-Knaus sterile period. Bartelmez (1937) has commented on the 1935 publication as follows: . . . "by excluding all relatively long or short cycles which could possibly be attributed to external influences like emotional upsets, infections, etc., and by an ingenious method of grouping his cases, [Latz] endeavors to minimize the extensive variability observed."

Part of King's (1933) study, already mentioned, was devoted to a report on 21 women engaged in industry at Rochester, N. Y., and Baltimore, Maryland. A total of 161 recorded cycles was collected, but difficulty was encountered with these women in maintaining a sustained interest in the keeping of proper records; this is shown by the fact that 11 individuals supplied not more than five cycles each. None was regular. The maximum departures from individual means ranged from one day (only five cycles recorded) to 26 days. Considering the small number of cycles per person, the variability shown is considerable.

*One exceptional record shows 9 out of 11 cycles as 28 days long and the other two as 27 days. The subject had been mentally deranged some years before; hence one wonders at the trustworthiness of this sequence even though it is possible to find segments of long-term menstrual records that approach this one in uniformity.

The other homogeneous group of women studied by King (1926; 1933) consisted of 33 Baltimore college undergraduates, graduate students, and instructors who supplied information concerning 716 cycles. The range of cycle lengths extended from 18 to 53 days and no individual was regular in any true sense over her respective observation period. The maximum variations from individual means varied from 2 to 20 days.

On the whole, the younger members (17 to 19 years) listed in King's tables show definitely more erratic records than do the older women. A greater variability in adolescents, before the rhythm is well established, has been mentioned by various writers, yet the exact degree of such variability remained unknown until Engle and Shelesnyak (1934) recently investigated this matter. They have published data obtained from 100 pubertal girls of a Jewish orphanage under conditions which should guarantee the accuracy of the records. At least 20 periods were obtained from each girl. The range in length of all cycles varied from 7 to 256 days, and the individual variability was high, as well. Although 28 days is the mode of all the cycles as a group, it is actually modal for only eight of the hundred individuals. Irregularity was found to decrease as menstrual experience increased. At the end of the first 20-24 cycles (mean terminal age, 15.5 years) the average standard deviation from the individual means was ±20 days. Thereafter, there was a progressive trend toward regularity; for example, when 40 to 44 cycles had been experienced (average terminal age, 16.4 years) the standard deviation for the total period since menarche was reduced to ±10 days. Ball (Hartman, 1936) also found a great irregularity in a study of adolescent girls at a state school near Baltimore. Hartman (1936) has emphasized this matter in an interesting and significant way by publishing beneath Ball's distribution diagram a second diagram, based on adolescent monkeys, which is strikingly similar.

Another study limited to college students (of philosophy and medicine), resident in university buildings, has been made by Scipiades (1935) at Budapest. Fifty women furnished data for eight months. No person was found to be regular; the extreme conditions are shown by two individuals who maintained their means in 43 per cent of their recorded periods and 38 women who on no occasion experienced their means.

It is possible that clinical patients, such as those previously mentioned, do not present ideal material for menstrual study, yet it must be admitted that their variability is no greater than in the college type just described. More pertinent are the objections which have been advanced against the representative nature of certain menstrual data obtained from nurses' training schools. This is because it is held as a well-recognized fact that a nurse's mode of life is conducive to marked menstrual irregularities and even to indefinite periods of amenorrhea.

Not admitting the validity of this criticism, Allen (1933) studied a group of student nurses at Chicago. The individuals were unselected, but detailed consideration may be limited to 110 whose 1,291 cycles were said to have been strictly controlled through a diligent, personal check-up prosecuted by the supervising nurse at the time of each expected monthly report. No subject proved to be actually regular, one in four was "absolutely irregular," while the extremes of cycle length ranged from 13 to 84 days. The six detailed, individual records which Allen gives as typical samples show great irregularity. It is of interest that 87 nurses, who at the beginning believed in their perfect regularity, actually were marked irregular. Fifty-three recognized that they were somewhat irregular but were astonished by the degree of irregularity brought to light.

More fully presented were the results furnished by Fluhmann (1934) on 76 California student nurses. It is possible that these subjects were better selected than Allen's, inasmuch as an elimination was made of individuals who were adjudged to show signs of menstrual disturbances due to the influence of their changed environment. A total of 747 cycles was collected over a period ranging from 6 to 13

months. The cycles varied from 11 to over 144 days in length, but 97 per cent of them were between 18 and 42 days long. The total spread was definitely more divergent than the corresponding values in Allen's series. Only five women kept within a five-day range between their shortest and longest cycles. Perhaps the relative youth of these nurses conspired with an occupational influence to produce this seemingly excessive irregularity.

Less homogeneous is a group of 50 nurses and office workers at Detroit who furnished 299 cycles, as described by Pratt and his associates (1929). At the start all considered they had regular periodicity. Yet when the records were finally disclosed, each was astonished at finding herself to have been in error. This group unfortunately consists of a mixture of adolescents and adults. Since the original records were not preserved it is not possible now to state what the distribution according to age actually was. In a letter, Dr. Pratt has written as follows: "None

TABLE IV. DETAILED DATA PERTAINING TO 8,812 MENSTRUAL CYCLES FURNISHED BY 644 WOMEN AND GIRLS. ALL THE CYCLES OF EACH GROUP WERE COMBINED AND TREATED AS IF BELONGING TO A SINGLE INDIVIDUAL

SOURCE OF DATA	MODAL CYCLE LENGTH (DAYS)	MEAN CYCLE LENGTH (DAYS)	AVERAGE DEVIATION OF CYCLES FROM GROUP MEAN (DAYS)*	STANDARD DEVIATION OF CYCLES FROM GROUP MEAN (DAYS)	PROBABLE ERROR OF STANDARD DEVIATION (DAYS)	CO-EFFICIENT OF VARIATION	PROBABLE ERROR OF CO-EFFICIENT OF VARIATION
1. Foster, 1889	--	28.0†	----	----	----	----	----
2. Issmer, 1889	28	27.8	2.09	2.93	0.13	10.54	0.46
3. Latz and Reiner, 1935	28	28.4	2.34	3.27	0.05	11.51	0.12
4. Latz and Reiner, 1937	27	27.3	2.21	3.65	0.05	13.37	0.17
5. King, 1933	27	29.1	3.13	5.46	0.21	18.77	0.71
6. King, 1926; 1933	27	27.7	2.59	3.68	0.07	13.29	0.23
7. Scipiades, 1935	29	30.2	3.42	7.17	0.19	23.74	0.63
8. Pratt, et al., 1929	28	26.6	2.22	2.81	0.08	10.56	0.29
9. Allen, 1933‡	29	28.2	2.89	3.77	0.08	13.37	0.28
10. Fluhmann, 1934	29	30.4	5.83	11.58	0.20	38.09	0.66
11. Engle and Shelesnyak, 1934	28	33.9	10.48	11.80	0.10	34.83	0.30
1-10. Means for adults	--	28.4	2.97	4.92	0.12	17.03	0.39
11. Means for pubertal girls	28	33.9	10.48	11.80	0.10	34.83	0.30

*In calculating the average deviations, the mean cycle length of each group was reduced to the nearest whole number (e.g., 27.5–28.4 was considered to be 28).

†It is impossible to decide what Foster meant by a 28-day mean; perhaps his statements merely refer to the 28-day standard so thoroughly assumed at that time. Hence the percentages in the first three columns of Table VI are given with reference to this 28-day average, whatever it may imply.

‡Some error has crept into Allen's work. Although 1,291 accurate periods were collected, only 511 (ranging from 17 to 40 days) were actually summarized in his Table III. It is obvious that the ones omitted from the ends of his series, which actually extended from 13 to 84 days, can account for but few of the missing 780 entries. In a personal communication Dr. Allen suggests that many of the original slips may never have been recorded on the permanent record and this loss was not detected subsequently. He believes from memory that the entries in his Table III are representative and it is these data that have been used for the details entered in Tables IV to VI of the present report. One can calculate proportionately that these 511 cycles were drawn from about 44 nurses. On the other hand, the more general data of the present Table III pertain to the full group of 110.

of the records included first menstruations. Most of the records were taken between the ages of 16 and 25." But since marked irregularity is a characteristic of the adolescent and is still pronounced at the nineteenth year (Table VII), one would expect part of the results to be as they are. The really significant feature, however, which gives this report value, is that all participants, regardless of age, were irregular.

The most recent publication on menstrual periodicity is by Gunn, Jenkin and Gunn (1937). This is the fullest and most careful investigation yet conducted on adults. A large number of British women (mostly of the professional classes) volunteered to mail record cards, month by month, showing the onset date of each mensis. The collection of data continued for one year. A total of 479 women provided information that can be considered reasonably reliable and 291 others furnished less complete data. The typical difference between the shortest and longest cycle is considered to be eight or nine days; in 30 per cent of the women it was over 13 days; in no case was it less than two to three days. The authors conclude: "The very regular case is either an absolute myth, or it is so rare as to be a medical curiosity."

The details which have been extracted and computed from these several investigations are presented in Tables IV, V, and VI. It should be noted that many of the items listed do not exist in the original pub-

TABLE V. DETAILED DATA PERTAINING TO MORE THAN 13,500 MENSTRUAL CYCLES FURNISHED BY 973 WOMEN AND GIRLS. THE RECORD OF EACH INDIVIDUAL IN A GROUP WAS FIRST TREATED SEPARATELY FOR MODE, MEAN AND DEVIATIONS AND THEN THESE WERE AVERAGED TO GIVE MEAN VALUES FOR THE GROUP AS A WHOLE

SOURCE OF DATA	MODAL CYCLE LENGTH (DAYS)	MEAN CYCLE LENGTH (DAYS)	MEAN AVERAGE DEVIATION OF CYCLES FROM MEAN (DAYS)	MEAN STANDARD DEVIATION OF CYCLES FROM MEAN (DAYS)	PROBABLE ERROR OF STANDARD DEVIATION (DAYS)	CO-EFFICIENT OF VARIATION	PROBABLE ERROR OF CO-EFFICIENT OF VARIATION
1. Issmer, 1889	28	27.8	2.11	2.56	0.35	9.49	1.31
2. Latz and Reiner, 1935	27; 28	30.8	1.42	1.79	0.08	5.81	0.27
3. Latz and Reiner, 1937	27	27.7	1.39	1.83	0.09	6.53	0.31
4. King, 1933	27	28.9	2.64	3.35	0.35	11.59	1.25
5. Gunn, et al., 1937	26	28.5*	----	4.09	0.09	14.10	0.30
6. King, 1926; 1933	27	28.4	2.04	2.59	0.21	8.98	0.75
7. Scipiades, 1935	29	29.9	----	----	----	----	----
8. Fluhmann, 1934	27; 29	32.4	5.06	6.50	0.35	20.03	1.08
9. Engle and Shelesnyak, 1934	29	33.6	----	14.28	0.68	42.50	2.03
1-8. Means for adults	27	29.3	2.44	3.24	0.22	10.93	0.75
9. Means for pubertal girls	29	33.6	----	14.28	0.68	42.50	2.03

*To make this average comparable with other means in the table, the value of 29.0 days, given by Gunn and his co-workers, has been reduced by 0.5 day. See footnote to Table II for the reason for doing this.

lications except as they lie concealed in the raw data. The grand means at the foot of all tables represent the averages of the individual items; these are simple means designed to show the average values of the several lots of data and intentionally do not attempt to weigh the uneven populations of the component groups. It seems unnecessary to comment specifically on the facts brought out by these tables. For the most part the meanings are clear. In any event, the significance of any portions that may not be apparent at first inspection should become intelligible after the appended section on statistical interpretation (p. 28) has been consulted. It is obvious that in comparing the corresponding data for different groups in Tables IV to VI one must also keep in mind the general, but pertinent, information contained in Table III.

TABLE VI. DATA ON THE DISTRIBUTION OF MENSTRUAL CYCLES WITH RESPECT TO GROUP MEANS AND INDIVIDUAL MEANS. THE TABULATION INVOLVES 8,812 CYCLES FURNISHED BY 644 WOMEN AND GIRLS

SOURCE OF DATA	OCCURRENCE OF CYCLES EQUALLING GROUP MEAN IN LENGTH %	OCCURRENCE OF CYCLES LONGER THAN GROUP MEAN %	OCCURRENCE OF CYCLES SHORTER THAN GROUP MEAN %	INDIVIDUALS NEVER EXPERIENCING OWN MEAN (% OF GROUP)	INDIVIDUALS EXPERIENCING OWN MEAN IN AT LEAST ONE-THIRD OF ALL CYCLES (% OF GROUP)	LOWEST MAXIMUM AND HIGHEST DEPARTURE FROM ANY INDIVIDUAL MEAN (DAYS)
1. Foster, 1889	11.9	59.2	28.9	----	----	----
2. Issmer, 1889	18.3	41.7	40.0	25.0	8.3	2; 12
3. Latz and Reiner, 1935	18.2	40.5	41.3	4.9	35.3	1; 22
4. Latz and Reiner, 1937	16.3	48.9	34.8	4.0	38.0	1; 53
5. King, 1933	9.3	50.9	39.8	33.3	23.8	1; 26
6. King, 1926; 1933	13.5	31.9	54.6	15.2	9.0	2; 20
7. Scipiades, 1935	9.1	52.8	38.1	76.0	5.0	----
8. Pratt, et al., 1929	12.4	39.5	48.1	----	----	----
9. Allen, 1933	11.0	47.5	41.5	----	----	----
10. Fluhmann, 1934	7.5	33.4	59.1	32.9	13.2	2; 69
11. Engle and Shelesnyak, 1934	2.7	11.6	85.7	33.0	1.0	6; 211
1-10. Means, etc., for adults	12.8	44.6	42.6	27.3	18.9	1; 69
11. Means, etc., for pubertal girls	2.7	11.6	85.7	33.0	1.0	6; 211

No previous writer has established clearly the degree of variability exhibited by different age groups. Only Gunn, Jenkin and Gunn (1937) have presented information on this topic. Yet the results of these investigators do not inspire confidence since they show the lowest variability among the young (13 to 22 years; standard deviation, ±2.01 days) and the highest variability at 23 to 27 years (standard deviation, ±7.01 days). But these conclusions with respect to young individuals are directly contrary to general experience. Especially are they at variance with the detailed study on pubertal girls conducted by Engle and Shelesnyak

(1934) who found the standard deviation for the first 22 cycles (mean terminal age, 15.5 years) to be ±20 days and for the first 45 cycles (mean terminal age, 16.4 years) to be ±10 days. However, the two sets of studies are not directly comparable since Gunn had access to only three records in the 13- to 17-year period.

In order to arrive at some firmer conclusion on the relation of variability to age, all the available data used in the present report were sorted into age groups and analyzed. In the furtherance of this Shelesnyak kindly supplied his original records on pubertal girls. It was desired to obtain information on the early, middle, and later periods of adolescence and on the definitely adult woman. Practically all the studies hereto-

TABLE VII. THE DEGREE OF MENSTRUAL VARIABILITY IN RELATION TO AGE. THE MEAN STANDARD DEVIATIONS IN EACH GROUP REPRESENT THE AVERAGE OF INDIVIDUAL MEANS

SOURCE OF DATA	NO. OF SUBJECTS	AGE RANGE OR CYCLE NO. SINCE MENARCHE (ALL INC.)	MEAN AGE OF SUBJECT	MEAN NO. OF CYCLES PER PERSON	MEAN STANDARD DEVIATION FROM MEAN (DAYS)	
Engle and Shelesnyak (1934)	26	1-22nd cycle	14.5*	22.0	20.0	
Engle and Shelesnyak (1934)	18	25-39th cycle	15.5†	15.0	10.36	
Fluhmann (1934)	21	18-19 yr.	ca. 18.5	10.3	5.48	mean, 4.35
King (1926; 1933)	14	18-19 yr.	ca. 18.5	8.9	3.22	
Fluhmann (1934)	15‡	22-27 yr.	23.1	10.4	2.67	mean, 2.27
King (1926; 1933)	33	22-35 yr.	26.6	18.4	2.24	
Issmer (1889)	10	22-39 yr.	28.1	10.0	2.37	
Latz and Reiner (1935; 1937)	200	22-49 yr.	31.4	12.2	1.81	
Gunn, et al. (1937)	336§	23-51 yr.	30.3	13.0	4.57	
Gunn, et al. (1937)	146‖	23-51 yr.	30.7	13.0	3.95	

*Age at the end of the eleventh cycle.

†Age at the end of the thirty-second cycle.

‡One very irregular record of only four cycles (standard deviation, ±35.34 days) was omitted.

§This constitutes Gunn's full group of reasonably reliable cases.

‖A selected group, with most relliable data, chosen by Gunn from the larger group of 336.

fore have been based on mixed groups of young and adult women (Table III), so that the conclusions given in Tables V and VI do not fulfill the present need. The results of these new calculations on the relation of variability to age are summarized in Table VII where decreasing variability with increasing age is shown clearly. Since Gunn's data are not in agreement with the general findings presented in this table, his figures have not been used in obtaining an average value for adults. If his larger value (±4.57 days) is included, then the mean standard deviation rises from ±2.27 to ±2.79 days; including his smaller select group, the average becomes ±2.61 days. It may be concluded that

two out of three menstrual cycles of the average adult woman may be expected to keep within a range of about 2.5 days above and below her individual mean.

Collateral evidence as to the general correctness of the fundamental conclusions concerning the existence of considerable variability in the human menstrual cycle comes from Hartman's (1932) close observations on his monkey colony; there, also, irregularity is the rule. For example, in 392 cycles from 22 selected females the distribution range extended from 14 to 42 days, with the mean set between 27 and 28 days and the mode at 28 days. As in the human being, the wide distribution of cycle lengths is due to the irregularity of each individual and not to differences between regular individuals. The average cycle length for different individuals ranged from 24.6 to 31 days; yet the irregularity exhibited in the detailed menstrual record of almost every animal was marked. Essentially similar evidence is to be found in the recent study of Elder and Yerkes (1936) on the sexual cycle of the chimpanzee. For 164 cycles of 11 presumably normal and mature animals the cycle length varied between 29 and 53 days; the average for all cycles was 36 days, the mode 35 days. The smallest difference between the shortest and longest cycle of any animal was 9 days; the largest difference was 23 days. Like the human female, both of these primates are not at all regular, and with the newer understanding of the factors governing menstruation one could scarcely expect it to be a wholly perfect mechanism, either in monkey or in man.

SUMMARY AND CONCLUSIONS

1. Only the records of consecutive menses, set down at the time of occurrence, are of value in studying the duration and variability of menstrual phenomena. Ordinary hospital histories, oral testimony, and similar data which depend on unaided memory cannot be given serious consideration since experience proves them to be utterly unreliable.

2. Some 20,000 calendar records from about 1,500 women and girls, as given in 12 different studies, have been assembled, corrected and analyzed.

3. The commonest length of 8,462 cycles (furnished by 585 persons) considered as a unit, is 28 days both for pubertal girls and adult women. The average length of all cycles is 33.9 days for girls and 28.4 days for women.

4. The commonest length of 17,652 cycles (the grand mode of the individual modes of 1,265 persons) is divided between 30 and 31 days for pubertal girls and is 27 days for adult women. The mean length of cycle, based on individual averages, is 33.6 days for girls and 29.5 days for women.

5. Statements concerning grand means and modes, however, have little significance in pubertal girls since they are so unrepresentative of the wide variability encountered.

6. The maximum departures of individuals from their means extends from 1 to 69 days in adults and from 6 to 211 days in pubertal girls.

7. The smooth frequency distribution, obtained from combining all the cycles of a group into one curve, is the result of overlapping individual irregularities and not of closely spaced, regular, individual performances.

8. The existence of favored, subordinate types of cycle length (such as 3, 5, 6 and 7 weeks), in addition to the modal type, do not appear either in the massed cycles of groups or in the records of individual performance. This is in sharp contrast to the conclusions based upon oral testimony.

9. In the first few years of the menstrual function the cycle length is extremely variable (7 to 256 days). It can be calculated that during the period of observation employed (averaging 31 cycles per person) one-third of the 100 pubertal girls never had a cycle that corresponded with their own means. Only one girl experienced her own mean as often as once in three cycles. From menarche to the twenty or twenty-fourth cycle, only two-thirds of the total cycles of an average individual kept within a 20-day range above and below her mean. Yet in middle adolescence, occupied by cycles 25 to 39, the regularity improved to such an extent that, on the average, two-thirds of all the cycles kept within a 10-day range.

10. At the end of adolescence, during the eighteenth and nineteenth years, the variability is still further reduced. In the 35 individuals studied, two-thirds of the cycles kept within a range of ±4.4 days with respect to the mean.

11. In several hundred adults more than 21 years old, a fluctuation of about ±2.5 days with respect to the mean expresses the limits of variability which contain two-thirds of all cycles. Expressed differently, an average adult woman must expect one-third of all her cycles to depart more than two days from her mean cycle length.

12. The amount of variability shown by adults is greater than ordinarily is credited. Cycles ranging from 2 or 3 weeks to 7 or more weeks appear in all of the groups (17 to 49 years) from which data have been collected. In the records of more than 500 women, 27 per cent never showed their own means during the observation period which averaged 11 cycles in length. Only 20 per cent experienced their own mean in at least one-third of their recorded cycles.

13. The adults, reported in detail by 11 different investigators, represent all ages from late adolescence to approaching menopause. They include American, Canadian, British, German, and Hungarian subjects, and they sample various grades of society. In no instance did an example of perfect menstrual regularity appear over any significant period of time; this is all the more noteworthy since many individuals had previously declared themselves to be the acme of invariability. The most regular records are short ones. In a separate (unpublished) study of menstrual records extending as long as 20 years, it will be shown that temporary successions of atypical regularity (or irregularity) may occasionally interpose themselves in a rhythm of fundamentally different characteristics. It is these unrepresentative fragments of the true record that sometimes lead to erroneous conclusions concerning an individual rhythm; even a record extending for over a year may prove to be unrepresentative.

14. In the face of all these facts it seems improbably that menstrual regularity, in any true sense of the word, ever will be encountered over

significant periods of time. Certainly, not the slightest evidence pointing toward perfect regularity has so far been produced for even a single exceptional individual. Should such a person be found at some future time, she will constitute a true medical curiosity.

15. Studies on the monkey and chimpanzee disclose menstrual irregularity comparable to that of the human being.

STATISTICAL METHODS USED AND THEIR INTERPRETATIONS

Data can be interpreted properly only through the use of proper statistical methods. Since many are unfamiliar with these methods, and especially with the interpretations to be made from such numerical findings, it seems desirable to explain the procedures used in the present study.

A. *Measures of the Central Tendency:*

1. The arithmetic mean (M) is the sum (Σ) of the separate variates (v) divided by the number of variates (N).

$$M = \frac{\Sigma\ v}{N}$$

2. The *mode* is the class with the greatest frequency.

B. *Measures of Variability:*

1. The *range* is the total spread of distribution from the lowest to the highest. It tells nothing about the shape of the distribution or the degree of concentration about the central tendency.

2. The *average deviation* (AD) is the average of the individual deviations from the mean (regardless of sign).

The individual departure of each variate from the mean (v - M) is found by subtraction. The sum of these is next obtained without regard to whether a deviation lies above or below the mean. Finally, this sum (Σ) is divided by the number of variates (N).

$$AD = \frac{\Sigma\ (v - M)}{N}$$

The average deviation of a normal distribution marks the limits of the middle 57.5 per cent of the measures. Applied to the present study, the chances are slightly better than even that the length of a random menstrual cycle will lie within the limits of the average deviation from the mean.

3. The *stand deviation* (σ) is the square root of the mean of the squares of the deviations from the mean.

To find this value, each individual variation from the mean is squared $(v - M)^2$; these are then summated (regardless of sign) and divided by the number of variates (N). Finally the square root of this mean value is extracted.

$$\sigma = \sqrt{\frac{\Sigma\ (v - M)^2}{N}}$$

The standard deviation of a normal distribution marks the limits of the middle 67 per cent of the measures. Applied to the present study, it may be expected that two cycles out of three will lie within the limits bounded by the standard deviation. Similarly, a variation equal to twice and thrice the standard deviation can be expected only once out of 22 and 370 cycles, respectively.

4. The *coefficient of variation* (CV) is a value obtained by reducing a standard deviation to an abstract number which then allows this particular standard deviation to be compared directly with any other standard deviation similarly treated. It is obtained by multiplying the standard deviation by 100 and dividing by the mean. Hence it expresses relative variability in terms of per cent of the mean.

$$CV = \frac{100\ \sigma}{M}$$

C. *Measures of Probability.*—

The *probable error* (PE) gives the measure of unreliability of any determination. It is a pair of values, one lying above and the other below the determination being

tested. The chances are even that the true value lies within the range of the probable error. The chances that the true value lies within ±2 PE are 4.6:1; similarly the chances that the true value lies within ±3 PE are 22:1.

1. The *probable error of the standard deviation* is obtained by multiplying the standard deviation by 0.67 and dividing by the square root of twice the number of variates.

$$PE_{\sigma} = \pm \frac{0.67\ \sigma}{\sqrt{2N}}$$

2. The *probable error of the coefficient of variation* is obtained by multiplying the coefficient of variation by 0.67 and dividing by the square root of twice the number of variates.

$$PE_{CV} = \frac{0.67\ CV}{\sqrt{2N}}$$

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The author studied rabbits which were subjected to general anesthesia by means of chloroform. He injected one group with anterior pituitary gonadotropic hormones and found that the duration of anesthesia was decreased but the recovery time showed no change. The effects of the injection of anterior pituitary hormone were almost identical with those produced by estrin. When the pituitary gland was irradiated with large doses of roentgen rays the duration of the anesthesia was increased and the recovery time decreased. Prominent regressive degeneration was observed in the pituitary gland and in the ovaries after strong irradiation of the pituitary gland with x-ray.

J. P. Greenhill.

RETINAL EXAMINATIONS

A Guide in the Management of the Toxic Hypertensive Syndrome of Pregnancy*

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APPROXIMATELY 10 per cent of pregnant women throughout this country exhibit some evidence of late toxemia of pregnancy, such as hypertension, albuminuria, and edema. Stander[13] and Peckham[9-11] independently arrived at this figure, and Peckham stated that this incidence was 17 per cent or greater among the pregnant women admitted to the maternity service at Johns Hopkins Hospital. Reports from various observers indicate that the percentage of women who have toxemia varies with the locality and living conditions. However, every physician attending a pregnant woman must be alert to detect symptoms of late toxemia of pregnancy and to undertake the management of various phases of this condition.

It has become increasingly evident that various conditions which formerly were grouped under the term, "albuminuria" of pregnancy, can be divided into those which were present prior to the pregnancy they complicate and those which arise in the course of pregnancy. It has been shown that chronic arterial disease and chronic nephritis (chronic glomerulosclerosis) antedating pregnancy are associated with pathologic findings and clinical syndromes which differ in many respects from those of late acute hypertensive toxemia which develops during pregnancy. For purposes of clarity in this paper, I shall use the terms "chronic arterial disease" or "chronic renal disease" to define antecedent conditions of this nature and "hypertensive" or "late toxemia of pregnancy" to define the acute late toxemia of pregnancy; the latter is subdivided into nonconvulsive, mild and severe toxemia (pre-eclampsia), and convulsive toxemia (eclampsia).

The majority of writers, in recent years, are agreed that pathologic and clinical findings in cases of acute late toxemia of pregnancy show evidence of more or less generalized vascular disease, primarily a condition of arteriolar spasm throughout the body. Acosta-Sison and others have presented evidence that vascular damage is the basis of the pathologic changes in the liver, kidneys, brain, and heart. Likewise, examination of patients suffering from severe nonconvulsive toxemia (pre-eclampsia) and convulsive toxemia (eclampsia) usually demonstrates the presence of spasm of the small arteries of the retina and of

*Read at a meeting of the George Washington University Medical Society, Washington, D. C., March 13, 1938.

Ophthalmoscopic examinations were performed by consultants of the Section on Ophthalmology.

the capillaries of the nail fold. Furthermore, in most instances, accurate retinal examination will reveal a distinct difference between the retinal changes produced by chronic vascular sclerosis or chronic nephritis and those present in cases of acute late toxemia of pregnancy. Cheney,[3] Wagener,[14] Hallum,[4, 5] and others reported that changes often occurred in previously normal retinal vessels in the course of late toxemia of pregnancy. Wagener made the important observation that acute vascular changes in the retina were sometimes superimposed on lesions characteristic of chronic vascular disease.

Addis accepted the hypothesis that arterial spasm is a frequent pathogenic factor underlying and uniting the various symptoms of late toxemia. He explained that the effects produced by angiospasm in the various organs may appear to be completely unrelated: in the brain, resulting in hypertensive encephalopathy; in the kidney, disturbance of function (glomerular vascular damage); in the liver, periportal thrombosis; in the subcutaneous tissue, anasarca. He suggested that these manifestations are the result not of varying causes but of the kind of tissue on which the single cause acts, and that vascular spasm is the factor which underlies and unites all the manifestations of pre-eclampsia and eclampsia.

Addis, Herrick, Irving, and others appear to be correct in emphasizing the role of vascular spasm in the production of the syndrome of toxemia, although the cause or causes responsible for the angiospasm have not been proved. Herrick stated that differences between the mild and more severe types of late toxemia are of degree, not of kind, and that the role of the kidney is not fundamental but is dependent on the vascular structure of its glomerular tufts and its copious blood supply as an excretory organ. If it is assumed, then, that in both the nonconvulsive and convulsive forms of the acute hypertensive toxemia of pregnancy, there is an underlying general systemic vascular spasm, we are prepared to accept hypertension as the important and outstanding symptom of this disease. Evidence strongly supports the supposition that hypertension is the result of generalized arterial spasm of undetermined cause and that the appearance of hypertension is preceded by functional spasticity of the glomerular, retinal, and other arterioles which, perhaps, would not be recognized in its incipiency.

In a broad sense, the degree of severity of acute hypertensive toxemia is measured more by the height of blood pressure than by any other symptom or finding. Also, permanent vascular and glomerular damage which may follow acute toxemia seem to depend on the height of the blood pressure and the length of time the hypertension, or the toxin producing it, is imposed on the vascular system. Follow-up studies, notably by Peckham, Herrick, and others have shown that chronic cardiovascular disease or chronic glomerular sclerosis occurs among many women as a direct consequence of acute hypertensive toxemia. According to Peckham and Stout, repeated examinations of patients whose condition was diagnosed as low reserve kidney (considered by many to be mild late toxemia of pregnancy) revealed that, five years later, approximately one-half of these patients had evidence of chronic arterial disease or chronic nephritis. This incidence rises with the height and duration of the hypertension, the condition being notably frequent among those whose systolic pressure registered more than 200 mm. of mercury.

Discussion of the management of acute hypertensive toxemia must include, also, consideration of chronic cardiovascular disease and chronic nephritis which antedate pregnancy. When definite chronic nephritis

or extreme hypertension is susceptible of diagnosis early in pregnancy, management of such a case often differs sharply from that of acute hypertensive toxemia, the symptoms of which appear later in pregnancy. Detailed descriptions of differential diagnosis and tests for renal function are not germane to the subject of this paper. However, inspection of the retina deserves mention, because evidence of chronic retinal arterial changes or nephritic retinitis may be demonstrable even when the results of tests of renal function are not diagnostic. If pregnancy is complicated by pre-existing chronic vascular sclerosis or chronic nephritis, there is a marked tendency toward exacerbation of the pre-existing disease in the first or early in the second trimester, and continuation of pregnancy usually results in a much more serious condition than before. Sometimes, patients who have so-called occult nephritis, which may not be susceptible of definite diagnosis prior to pregnancy and some who have mild hypertension may pass through pregnancy without superimposed toxemia.

I have reviewed the pathogenesis of conditions classified as late toxemia of pregnancy, because the concept that more or less prolonged acute, general, vascular spasm is responsible for permanent cardiovascular and glomerular injury, which may follow toxemia of pregnancy, has emphasized the need for the termination of pregnancy in certain of these conditions. In addition to readings of the blood pressure, results of examinations of the urine, evaluation of subjective symptoms and, occasionally, chemical examinations of the blood, a valuable index of the degree of spasm of the vascular system and the rate at which this spasm is progressing, is furnished by changes observed in the vessels of the retina. In a previous paper I noted that, in the course of routine ophthalmoscopic examination of pregnant women, Masters found that, in every case in which the blood pressure was elevated to 150 mm. of mercury or more, there was narrowing of the caliber of the retinal arteries. Among 44 cases of toxemia, he observed this retinal change in 3 cases in which the blood pressure was initially less than 150 mm. of mercury but subsequently rose much higher. Wagener found there were retinal changes in 70 per cent of pregnant women whom he examined, and whose systolic blood pressure was more than 140 mm. of mercury. Later Hallum quoted similar findings.[4]

Wagener also states: "In cases of toxemia of pregnancy in which there is an associated rise in blood pressure, changes in the arterioles appear first and those in the retina proper, commonly called 'retinitis' are secondary to and apparently dependent on, the changes in the arterioles. The caliber of the arterioles appears narrowed and the lumen is reduced because of spastic contraction and increased tonus of the walls of the arterioles. This change in the arterioles may disappear entirely if there is early and permanent fall in blood pressure. The constriction soon becomes fixed if the toxemia progresses. When the constriction of any arteriole becomes so fixed and severe as to cause secondary capillary ischemia or stasis, localized edema and hemorrhage appear in the adjacent retina. If the toxemia continues, this spastic constriction may become so generalized and severe as to produce diffuse retinitis of the albuminuric type, the classic 'retinitis of pregnancy nephritis.' The presence or absence, or the advancement of the involvement of the arterioles can be determined best by frequent systematic examination of the retina."

It was found that Wagener's description of the retinal changes in cases of acute toxemia of pregnancy could be divided into four stages or grades, related to the severity and duration of the hypertension: Grade 1, the first sign of which is spastic narrowing of the arterioles of the retina, which may affect all branches of the central artery; Grade 2, in which irregular constriction of the lumens of the arterioles usually appears first or to a more severe degree in smaller nasal branches, sometimes varying in situation or degree from day to day; Grade 3, in which narrowing and constriction are more fixed and individual cotton-wool patches and hemorrhagic regions may appear in the retina; and Grade 4, in which diffuse retinitis of the albuminuric type is found. By the use of this system of grading of progressively severe retinal changes, a tabulation, previously reported, was made of the retinal examinations of 108 patients who had late toxemia of pregnancy; in 14 of these cases, there was pre-existing hypertension. The data indicated that (1) all patients who had a systolic blood pressure of 200 mm. of mercury or higher had evidence of acute retinal changes, most of them severe, (2) 90 per cent of the patients who had a systolic blood pressure between 170 and 200 mm. of mercury had retinal changes, and (3) only 52 per cent of those whose systolic pressure was less than 160 mm. of mercury had retinal changes, which were predominantly mild in character. It was shown also that there was a progressive relationship between the higher systolic blood pressure and more severe changes in the retinal arterioles. Comment was made that, in a number of cases, the retinal arteriolar changes were the deciding factors in determining if, and when pregnancy should be terminated. Hallum recently stated: "The obstetrician will find that a study of the eye grounds, when considered with the other signs of toxemia, will be a real aid, probably the most consistently reliable single guide in determining when pregnancy should be terminated."

As this paper is concerned with the influence of retinal examinations on the management of late toxemia of pregnancy, other phases of treatment will not be considered in detail. In brief, the objects of treatment are, first, to reduce the incidence of late toxemia and eclampsia, second, to prevent mild toxemia from becoming severe, third, to effect improvement in toxemia which has become severe, and fourth, to shorten the course of the disease. Shortening the duration of toxemia by spontaneous or artificial termination of pregnancy usually is followed by relief of symptoms and cessation of the toxemia. When symptoms of toxemia are detected early, the institution of appropriate measures may avert progression. In spite of treatment, mild symptoms may become severe or the patient may be observed for the first time with symptoms of severe toxemia. Her condition may approach so nearly the eclamptic state that measures to avert convulsions must be carried out urgently. Sedation, dietary restriction, limitation of fluids, careful use of solutions of glucose or magnesium sulfate, or both, will be followed usually by somewhat lowered blood pressure, increased output of urine and lessened edema. When toxemia is severe and when the patient fails to improve, or when, following improvement, there is a relapse, termination of preg-

nancy is indicated in the interest of the mother. However, gestation may have reached so nearly the time at which there is a reasonable chance for the fetus to survive, that delay in the interest of the fetus is most desirable.

The probability of survival among babies born of women suffering from toxemia is less than normal and this is especially the case when the babies are premature. The fetus may die in utero, if overwhelmed by maternal toxin during the course of severe toxemia. Also, as previously stated, the number of women who have chronic arterial disease and chronic nephritis as a consequence of late toxemia of pregnancy, increases proportionately to the height of the blood pressure and duration of the toxemia. A nicety of judgment may be required in deciding whether pregnancy should be terminated and in selecting the proper time and method of interruption.

The method of terminating pregnancy depends on a number of factors, including age, parity and condition of the patient, duration of pregnancy, adequacy of the bony passage, and condition of the cervix.

For reasons previously stated, in the interest of both mother and fetus, the optimal time for terminating pregnancy must be selected carefully. This decision must rest chiefly on the period of gestation and the duration and severity of the toxemia. Evaluation of the severity of the toxemia depends mainly on subjective symptoms of headache, visual disturbance, epigastric pain and such clinical findings as hypertension, albuminuria, and edema. The reliability of chemical examinations of the blood to determine the severity and progress of such toxemia is debatable. When the toxemia is comparatively mild and when the systolic pressure is less than 150 or 160 mm. of mercury, the necessity of terminating pregnancy arises rarely; when the patient is in the most severe nonconvulsive stage and has a blood pressure of about 180 mm. of mercury or more, induction usually is indicated; when the patient is in the moderately severe stage and has a systolic blood pressure of 160 to 180 mm. of mercury, the problem if and when labor should be induced may be most perplexing. In nearly all such cases, examinations of the retina will reveal changes in the retinal arteries. Those skilled in the use of the ophthalmoscope usually can determine whether these changes are a residuum of pre-existing arterial or glomerular disease, whether they are characteristic of acute toxemia, or whether the acute changes are superimposed on old arterial sclerosis. Repeated examinations determine whether acute vascular changes are advancing, receding, or stationary.

For the past fifteen years, information obtained from examination of the retina has been increasingly useful to us in the management of late toxemia. This information often has influenced the obstetrician to decide for or against termination of pregnancy. For example, interruption of pregnancy has been undertaken when retinal examination gives evidence of advance in the vascular lesion, although there has been no untoward change, or, perhaps, apparent improvement has occurred in the patient's clinical condition. Induction of labor on this additional evi-

dence, we believe, has averted an increase in severity of toxemia in a number of cases. In other cases, interference has been avoided when retinal examination has revealed either a normal retina or, on repeated examination, no advance of the acute vascular spasm, or perhaps evidence only of previous arterial changes. Such evidence often has permitted further observation and delay, thereby increasing the chances of survival of the fetus without needlessly jeopardizing the mother.

Retinal examination prior to delivery was recorded in this series of 167 patients who had hypertension and other symptoms of late toxemia of pregnancy. Examination of 117 of these patients revealed varying degrees of arterial spasm characteristic of acute toxemia, 23 had evidence only of chronic vascular sclerotic change characteristic of pre-existing cardiovascular disease, and 27 gave no demonstrable evidence of a retinal lesion. Nearly all of the last group had comparatively mild toxemia. Including those patients with chronic changes, 83 per cent on examination gave evidence of retinal involvement. The percentage of cases in which there was evidence of changes in the retina increased directly with the height of the blood pressure. The incidence of patients whose retinas had undergone changes, with the corresponding blood pressures is as follows: 51 per cent, never more than 150 mm. of mercury, 84 per cent, between 150 and 169 mm., 92 per cent, between 170 and 199 mm., and 100 per cent, 200 mm. or more.

Although the presence of retinal changes was of diagnostic value in 140 cases or 83 per cent of the entire series, it is not our intention to imply that the degree of vascular spasm was the sole determining factor on which the decision of whether or not to interrupt pregnancy was based. Among the more severe cases of toxemia and among cases of eclampsia, the symptoms and condition of the patient frequently indicate the need for termination of pregnancy. However, there are many cases of late toxemia in which a drop in blood pressure and lessened edema occur following rest, sedatives, and diuresis. The blood pressure may not be alarmingly high and the patient may not feel particularly ill. In such cases, frequent, sometimes daily, examinations of the retina may reveal progressive changes, which presage a similar advance of generalized arteriolar involvement before the appearance of a further rise in blood pressure or other significant symptoms. In 51, or 43.5 per cent, of the 117 cases, evidence of a progressive increase in retinal arteriolar spasm was an influencing and, frequently, a deciding factor in the decision to terminate pregnancy. Spontaneous onset of labor decided the problem in many additional instances. Among 22, or over 18 per cent, of the cases, the retinal changes were stationary or had regressed. These findings directly influenced the decision that the safety of the patient was not jeopardized unduly by deferring interruption of pregnancy in the interest of the fetus. Also, among a group of some 12 patients whose systolic pressures ranged from 150 to 200 mm. of mercury, the absence of any evidence of vascular change undoubtedly influenced the decision not to terminate pregnancy. Among some of the 23 patients who had pre-existing hypertension, many of whom were not

seen early in pregnancy, the differential diagnosis between chronic arterial disease and acute toxemia was made possible by retinal examination which revealed chronic rather than acute vascular lesions.

In this series of cases of late toxemia of pregnancy, the first examination of the retina was recorded in 1922. Since that time the Section on Ophthalmology at the Mayo Clinic has cooperated fully in carrying out these examinations. The presence and degree of spasm of the retinal arteries has paralleled so closely clinical evidence of the severity of toxemia that we have increasingly depended on this examination. Dividing these fifteen years into three five-year periods, it is noteworthy that retinal examination has been a distinct guide to the management of late toxemia of pregnancy in approximately 28 per cent of the cases in the first five-year period, in 51 per cent in the second five-year period, and in 56 per cent in the last five years.

COMMENT

The weight of evidence indicates that acute late toxemia of pregnancy presents a hypertensive syndrome which is characterized by generalized spasm of the smaller arteries. The degree of systemic vascular spasm appears to parallel the height and duration of the blood pressure and the severity of the toxemia. Examination of the arterioles of the retina reveals changes which apparently manifest the degree of angiospasm throughout the body. In addition to hypertension and other symptoms, the presence and persistence of noticeable retinal vascular spasm is a guide in the management of late toxemia. This finding often indicates the need of avoiding further generalized and, perhaps, permanent vascular damage by using measures to terminate pregnancy when the condition of the patient permits. On the contrary, the presence of retinal changes of comparatively mild degree, or the absence of such changes, may indicate that pregnancy may be allowed to continue in the hope of obtaining a living infant without unduly jeopardizing the safety of the mother.

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URIC ACID METABOLISM IN ECLAMPSIA

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IT IS well established that eclampsia is accompanied by a definite elevation in blood uric acid,[11, 19] although the concentration of the other known nitrogenous elements may remain within normal limits. The significance of this observation is as yet not known, not even so far as it may or may not be associated with the etiology of this disease, about which we are still ignorant.

In birds and reptiles nitrogenous waste products are excreted chiefly in the form of uric acid, a process probably associated with an adaptation to urgent need of water preservation in arid regions. In mammals, on the other hand, these end-products of nitrogen metabolism are chiefly excreted in the form of urea, which, apart from water, is the main constituent of human urine.

In man the formation of uric acid is chiefly from nucleoproteins, exogenously from the purines in the ingested food and endogenously from the nucleoproteins of body cells. In addition, synthesis of uric acid may occur, the nitrogen source being ammonia or amino acids, according to Schuler and Reindel.[9] The carbon source for such synthesis is still unknown. The disintegration of nucleic acid depends upon several steps and enzymes, the final step in man being the oxidation of xanthine to uric acid. Unlike the case in lower animals, in the human uric acid is most probably not destroyed to allantoin unless to an exceedingly small extent. Wiechowski[16] found only 10 to 15 mg. of allantoin per day, as compared with 300 to 500 mg. of uric acid in the urine of man. The source of xanthine oxidase in man, necessary for the formation of uric acid, is in the liver, and thus it has been assumed that uric acid formation takes place wholly in the liver. There may, of course, be other methods of formation, although at present there is no evidence in support of such an assumption. That some uric acid destruction occurs in man is still a controversial problem, although the weight of evidence is in favor of such a conclusion. The end-product of such destruction is unknown, unless it be urea. It is also probable that excessive uric acid may be excreted to some extent into the bowel where disintegration by intestinal bacteria may take place. In dogs uricolysis occurs, and undoubtedly the site of this destruction is the liver as proved by the accumulation of uric acid after liver extirpation experiments by Bollman, Mann and Magath,[2] as well as by the quantitative experiments on allantoin by Schittenhelm and Chrometzka.[8]

The mechanism of uric acid excretion through the kidneys is still not quite clear. Berglund and Frisk[1] conclude that only a small part of the blood uric acid is filtrable, although Homer Smith[10] is of the opinion that uric acid is filtrable from human blood and attributes its failure to be excreted to tubular reabsorption. As normal kidneys concentrate urea about 80 times and uric acid only about 20 times, it has been supposed that uric acid is less easily excreted by the kidneys, especially when diseased, than are the other chief nitrogenous constituents. This assumption, however, is not supported clinically, as uric acid is not the first of the nitrogenous substances to be retained in nephritis. The normal kidney concentration factor, in the case of uric acid, is probably that low because of tubular reabsorption, as suggested by Homer Smith.

Rangier[7] believes that uric acid appears in the urine in the form of a ureide compound together with urochrome, a theory which will explain its great solubility.

Following the discovery of uric acid in 1776 by Sheele, Fourcroy was able to oxidize this substance, by means of chlorine water, to urea. The constitution of the purine group was worked out in great part by Emil Fischer. In 1902 Wiener showed, by means of feeding urea and 3 carbon acids to birds, the metabolic relationship of uric acid to urea and lactic acid. The two isomers of uric acid, formed by shifts of "H" atoms, were named lactim and lactam by Baeyer, and it is probable that in the blood, uric acid occurs as a mixture of these two isomers.

The uric acid content in human blood may be influenced by the amount of purines and also fat in the diet. Harding and his co-workers have shown that diets high in fat, resulting in ketosis, increase the amount of uric acid in the blood. This may be due partly to decreased elimination, resulting from concentration of the blood following high fat diet. Quick[5] has shown that uric acid excretion may be depressed by ketosis, by lactic acid, and aceto-acetic acid, in other words, by substances that reduce the formation of glucuronic acid. Lewis and Karr[4] showed that benzoic acid very definitely decreases the excretion of uric acid. On the other hand, substances which stimulate the production of glucuronic acid, such as pyruvic acid, increase the excretion of uric acid.

It is interesting to note that Quick[6] has recently found that in certain liver ailments, the depressing effect of benzoic acid on the excretion of uric acid is markedly augmented. It should also be pointed out that when nucleoproteins are excessively destroyed, as in leucemia and pneumonia, the uric production is increased.

The amount of uric acid in the blood of man, under normal conditions and a regulated diet, varies between 2.5 and 4.5 mg. per 100 c.c., according to the methods of Folin and Benedict. However, as yet, we do not know exactly how closely the results obtained by these methods approximate the actual amounts in the blood, and, therefore, the standards used in any study are dependent upon the method of analysis employed. The distribution of uric acid between cells and plasma evidently may vary considerably. Theis and Benedict[14] were unable to detect any constancy in the relative distribution.

The amount of uric acid excreted by an adult on a purine-free diet varies between 0.3 and 0.5 gm. per day. Burian and Schur[3] believe that the source of the endogenous uric acid is the oxidation of the hypoxanthine of the muscles, and are of the opinion that the amount excreted represents only about 50 per cent of that formed in the body, from either exogenous or endogenous sources. This question of uric acid destruction in man is, of course, still an unsettled problem. Wells[15] reported a case of bichloride poisoning with almost complete anuria for nine days, where there was no accumulation of blood uric acid, although the tissues contained relatively large amounts of uric acid, while the liver showed only 1 mg. per 100 gm. of tissue. From this observation, as well as from the results of uric acid injection experiments, it seems that a certain amount, 30 per cent or more, of uric acid is normally destroyed and that this probably occurs in the liver.

In order that we may perhaps obtain an understanding of the high blood uric acid values in eclampsia, repeated blood and urine uric acid determinations were performed in five eclamptic patients. In all in-

stances twenty-four-hour urine specimens were collected for the analyses. The periods of chemical study in these women varied from eight to twenty-one days. For the uric acid analyses in the urine we employed the method of Benedict and Hitchcock and for those in the blood, that of Folin.

In Chart 1 are plotted the averages of the findings of the routine chemical analyses of the blood in 132 consecutive eclamptic patients. A study of this chart substantiates the statement, made above, that the blood uric acid in eclampsia is

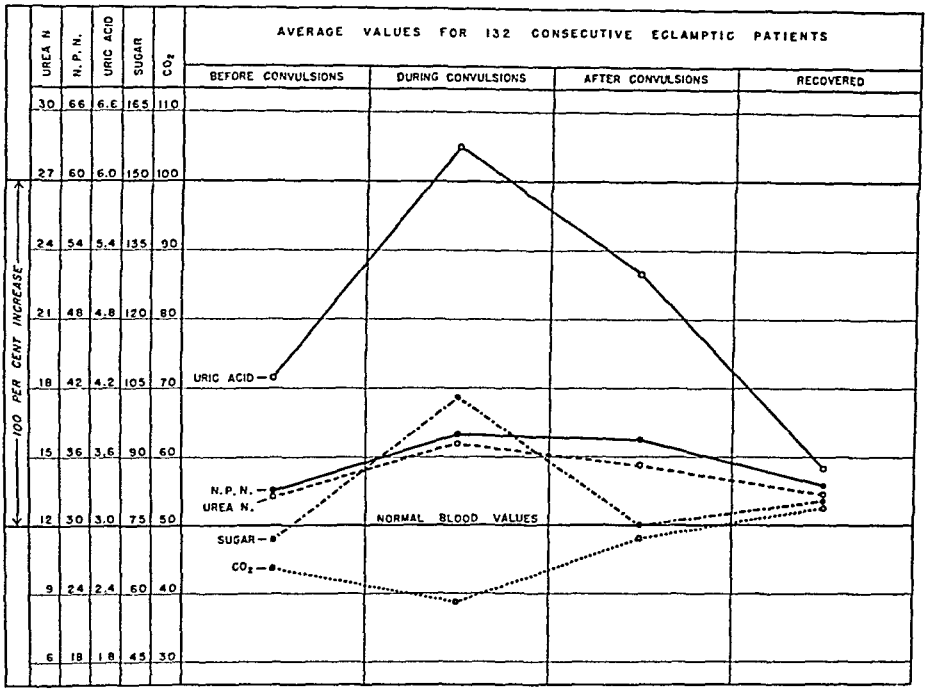


Chart 1.—Average values for 132 consecutive eclamptic patients.

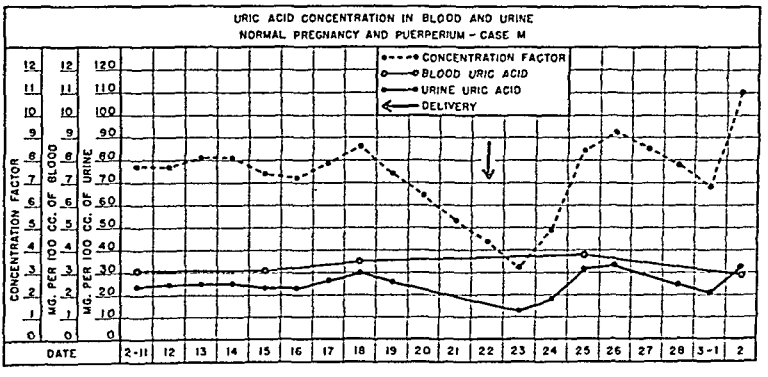


Chart 2.—Uric acid concentrations in blood and urine. Normal pregnancy and puerperal. Case M.

definitely increased, although the concentrations of the urea nitrogen and the non-protein nitrogen show no similar elevation. This increase shows in the early development of the disease is most marked during the period of convulsions and disappears after full recovery.

Chart 2 represents a study of the uric acid concentration in the blood and urine in a control, a normal pregnant woman, over a period of twenty-nine days, covering the last three weeks of gestation, labor, and the first week of the puerperium. The uric acid in the blood and the urine, is plotted in milligrams, per 100 c.c. of blood

and per 100 c.c. of urine, respectively. The curves show the remarkable constancy of uric acid concentration in both blood and urine. A third curve is shown, representing the concentration factor, obtained by dividing the urine concentration by that of the blood. It will be noted that this factor is likewise fairly constant, fluctuating downward only at the time of delivery.

In Charts 3, 4, 5, 6, and 7 are shown the uric acid concentrations in the blood and urine of the 5 eclamptic patients. The concentration factor for uric acid,

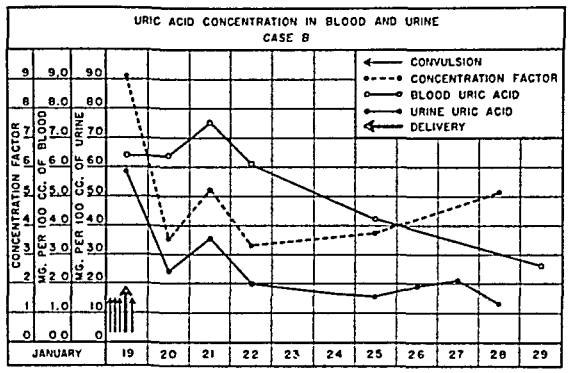


Chart 3.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case B.

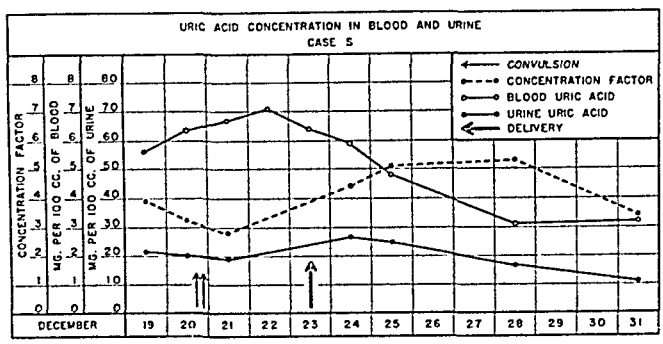


Chart 4.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case S.

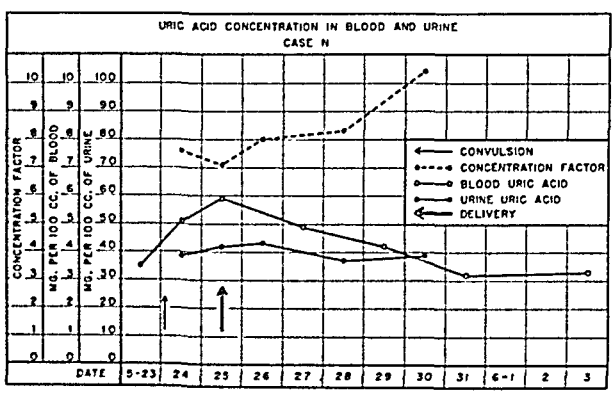


Chart 5.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case N.

calculated in the manner described above, is plotted for each patient, while the charts also indicate the number and time of convulsion and the time of delivery. In 4 of the patients the eclampsia was of the antepartum type, while in one it occurred in the puerperium (post-partum eclampsia). A study of these 5 charts reveals the high blood uric acid during the convulsive period, the rather constant and

unimpaired uric acid excretion as shown by the concentration in the urine and, lastly, that the uric acid concentration factor is not below the normal limits during the height of the disease. In one case (Chart 3) the concentration factor appears to be highest at the time of convulsions, while in another (Chart 5) it is highest at the time of complete recovery.

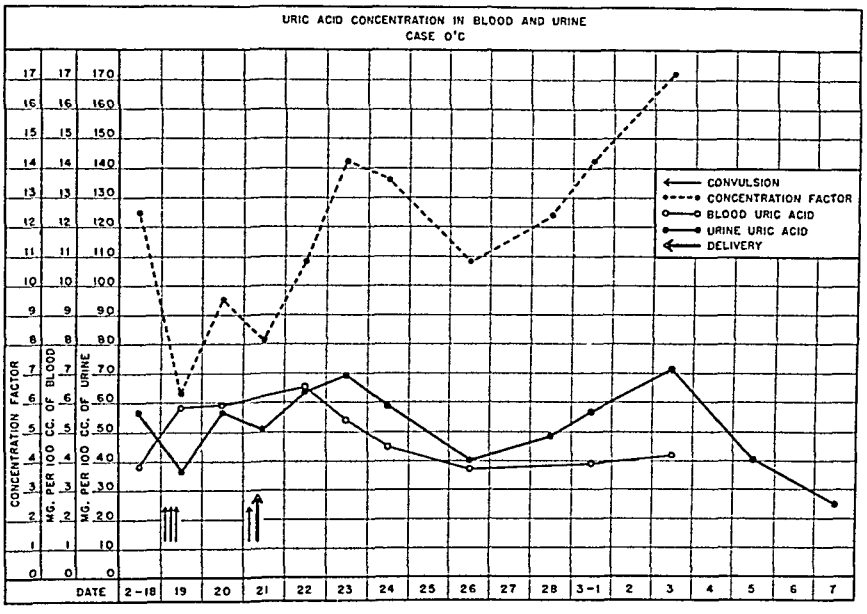


Chart 6.—Uric acid concentrations in blood and urine in ante-partum eclampsia. Case O'C.

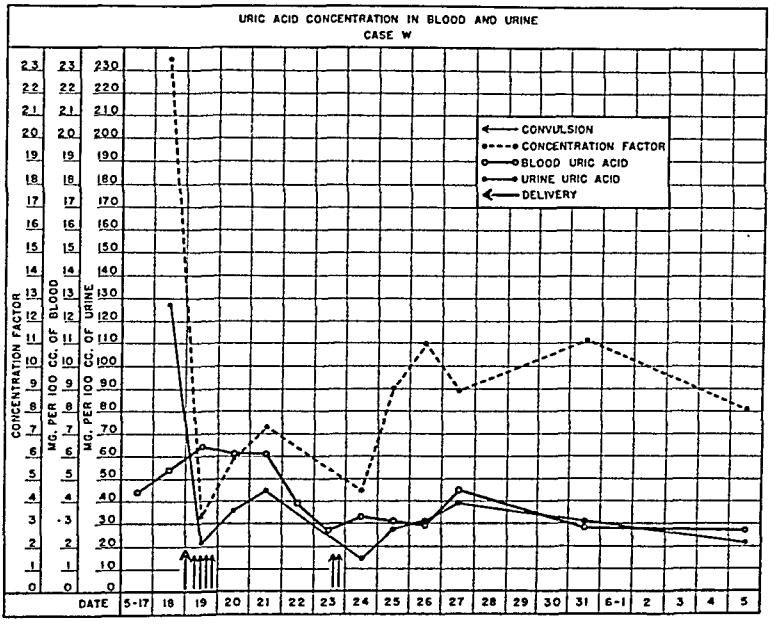


Chart 7.—Uric acid concentrations in blood and urine in post-partum eclampsia. Case W.

A composite chart (Chart 8) has been prepared using the average values in the four cases of antepartum eclampsia at the time of convulsions and delivery, and at daily intervals preceding and following this period of acute involvement. The resulting curves corroborate the interpretations we have placed on the individual charts. It seems a justifiable conclusion that the kidney concentration factor for uric acid is not decreased during the eclamptic seizure and furthermore, is not at a lower

level than at the time of complete recovery, as indicated by the value on the eighth day following delivery. In other words, uric acid excretion does not appear to be impaired, to even a minor extent, in patients suffering from eclampsia.

As we wished to compare the concentration of uric acid in the blood with that in the urine, we have presented, in the above charts, the amount of uric acid in 100 c.c. of urine, although the total amount of

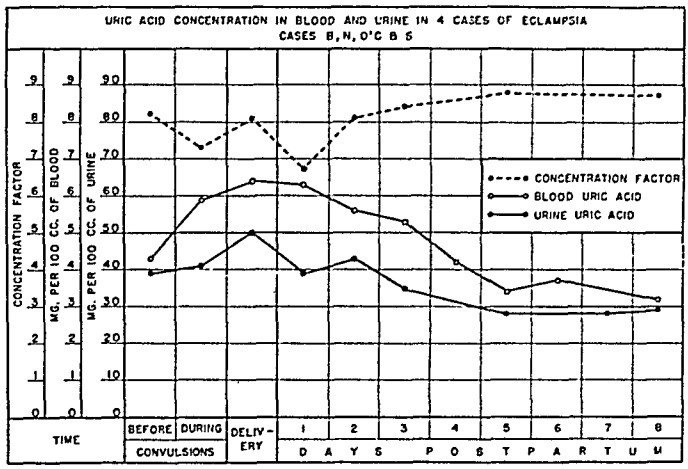


Chart 8.—Uric acid concentrations in blood and urine in four cases of ante-partum eclampsia. Averages.

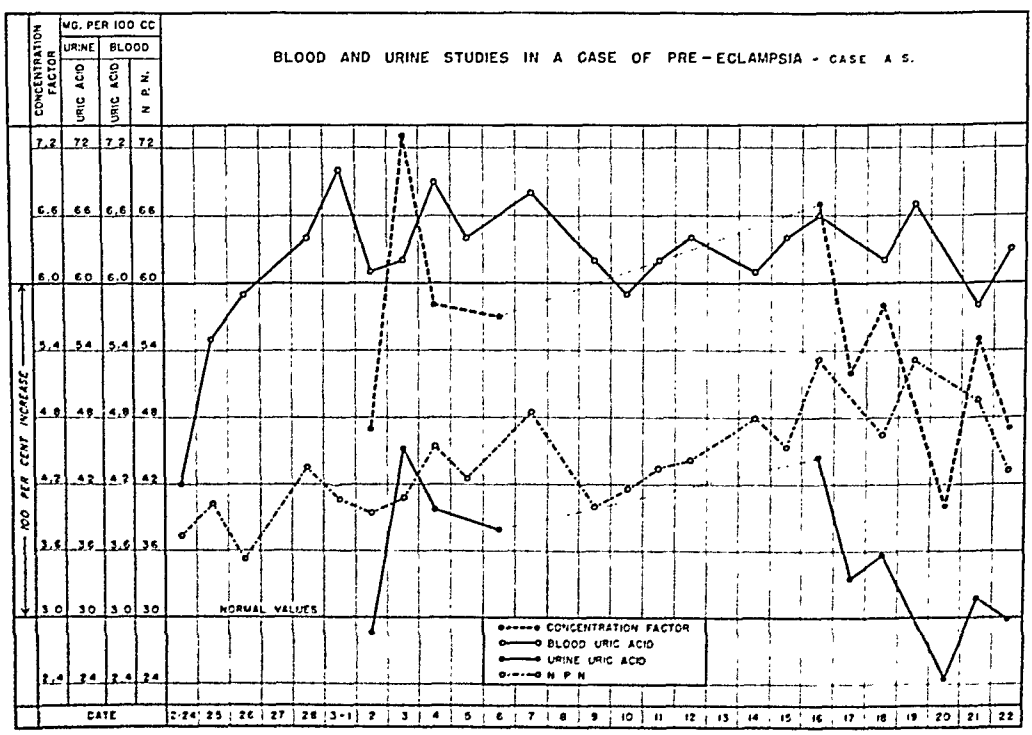


Chart 9.—Uric acid concentrations in blood and urine and nonprotein nitrogen in blood in case of pre-eclampsia.

uric acid excreted in each twenty-four-hour period studied was determined in all instances. These total amounts of uric acid, excreted daily by the five eclamptic patients, are shown in Table I. The individual, as well as the average, amounts excreted are within the normal limits as given in the earlier part of this paper.

TABLE I. TOTAL URIC ACID EXCRETION, EXPRESSED IN GRAMS PER 24 HOURS

CASE		DAYS ANTE-PARTUM PERIOD			DAY OF DELIVERY	DAYS POST PARTUM														
		3RD	2ND	1ST		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
S	Convulsion	2																		
	Uric acid	0.36	0.41			0.56		0.30	0.37	0.46	0.46	0.35	0.37	0.32				0.31		0.29
B	Convulsion				4															
	Uric acid				0.56	0.71	0.47	0.76		0.62	0.64	0.70	0.51	0.34						
O'C	Convulsion		3		1															
	Uric acid	0.39	0.13		0.27	0.95	0.90	0.33		0.46		0.57	0.46		0.28			0.33		
N	Convulsion			1																
	Uric acid				0.18	0.30	0.80		0.71	0.24										
	Convulsion				3															
	Uric acid				0.74	0.45	1.04	0.37	0.06	0.18	0.31	0.59	0.52	0.39	0.27	0.65	0.31	0.36	0.38	
Average uric acid		0.38	0.27		0.44	0.59	0.80	0.44	0.38	0.39	0.47	0.55	0.47	0.35	0.28	0.65	0.31	0.33	0.38	0.29

We have had an opportunity to study a patient with pre-eclampsia over a period of a month. During that time 21 blood specimens were obtained and analyzed for nonprotein nitrogen, urea nitrogen, uric acid, chlorides, CO_2-combining power and sugar. Twenty-four-hour specimens of urine were analyzed for uric acid. In Chart 9 are shown the findings for blood nonprotein nitrogen and uric acid and for urine uric acid. The other constituents determined are not shown in the chart, as they were wholly within normal limits. A study of the patient's past history, antenatal course in this pregnancy, blood pressure, albuminuria, edema, eye ground findings and symptoms, leaves no doubt that she is suffering from pre-eclampsia. The patient is still undelivered and about three weeks from term (April, 1938). The chart of this pre-eclamptic patient reveals an elevation of blood uric acid which is constant and persistent, although the hypertension, albuminuria, edema, and symptoms had responded to treatment. The nonprotein nitrogen of the blood is at the upper limits of normal while the excretion of uric acid is within normal range and certainly not decreased. The diet has been uniform and purine-free during the major part of the period of study.

We regard pre-eclampsia as the same disease entity as eclampsia, differing from the latter only in that it is not accompanied by convulsions. However, pre-eclampsia usually eventuates into eclampsia, unless the patient responds to treatment, whether that be sedation or delivery. Viewing pre-eclampsia, then, as a mild or early stage of actual eclampsia the persistent elevated blood uric acid curve in this last chart assumes a certain significance with respect to the metabolic disturbance which may be the basis of the development of eclampsia. This change in uric acid metabolism occurring previous to the outbreak of eclamptic convulsions and resulting in a high blood uric acid, due either to increased formation, or more likely, to decreased destruction of uric acid in the liver, is thus far the earliest perversion of metabolism noted in the development of eclampsia. Normal pregnancy is accompanied by certain marked changes in metabolism, such as, among others, a lowering of the total base, an increase in total lipids and decrease in the CO_2-combining power of the blood and a depression of urea in both the blood and urine. However, these changes are not any more pronounced in eclampsia.

We finally present Chart 10, which shows the values for nonprotein nitrogen and uric acid in the blood of a fatal case of eclampsia. The autopsy findings in this case showed the kidneys to be normal and the liver to have peripheral necrosis of the lobules. The autopsy report reads as follows: "*Liver:* The liver weighs 1,450 gm. The capsule is smooth and glistening. The liver is slightly softer than normal. The external surface of the liver is a light reddish brown mottled with a few small areas of red mainly over the surface of the right lobe. On cut section the cut surface is a light brown mottled with minute areas of red. Scattered throughout the liver substance are a few areas of grayish yellow in which the liver architecture is lost. These areas measure from 1 to 2 cm. across.

"*Kidneys:* The right kidney weighs 135 gm., and the left 140 gm. The capsule of the right kidney is smooth and glistening and strips with ease. The external surface of the right kidney is a pale pinkish brown. On cut section the cut surface is a pale pinkish red. The cortex is of normal thickness and sharply demarcated from the medulla. The mucosa of the pelvis of the right kidney is slightly thickened and presents areas of red in which the mucosa is granular. The right ureter is slightly dilated. The left kidney is similar to the right. The left pelvis and ureter are normal." The curves in Chart 10 show the nonprotein nitrogen to be within normal limits, excepting immediately before death, when there was a slight elevation

to 48 mg. per 100 c.c. of blood. The uric acid, on the other hand, was elevated throughout the period of study and rose to approximately three times the normal value. As the postmortem examination revealed normal kidneys and the blood analyses showed no nitrogenous retention during the first two days of the disease, it would appear that the elevated uric acid in the blood was not due to lowered kidney excretion of this substance.

DISCUSSION

From the findings presented above, it seems to us, that the increased blood uric acid in eclampsia cannot be explained on the basis of decreased excretion by the kidneys. It is also noteworthy that the increase in blood uric acid appears as one of the early signs of the

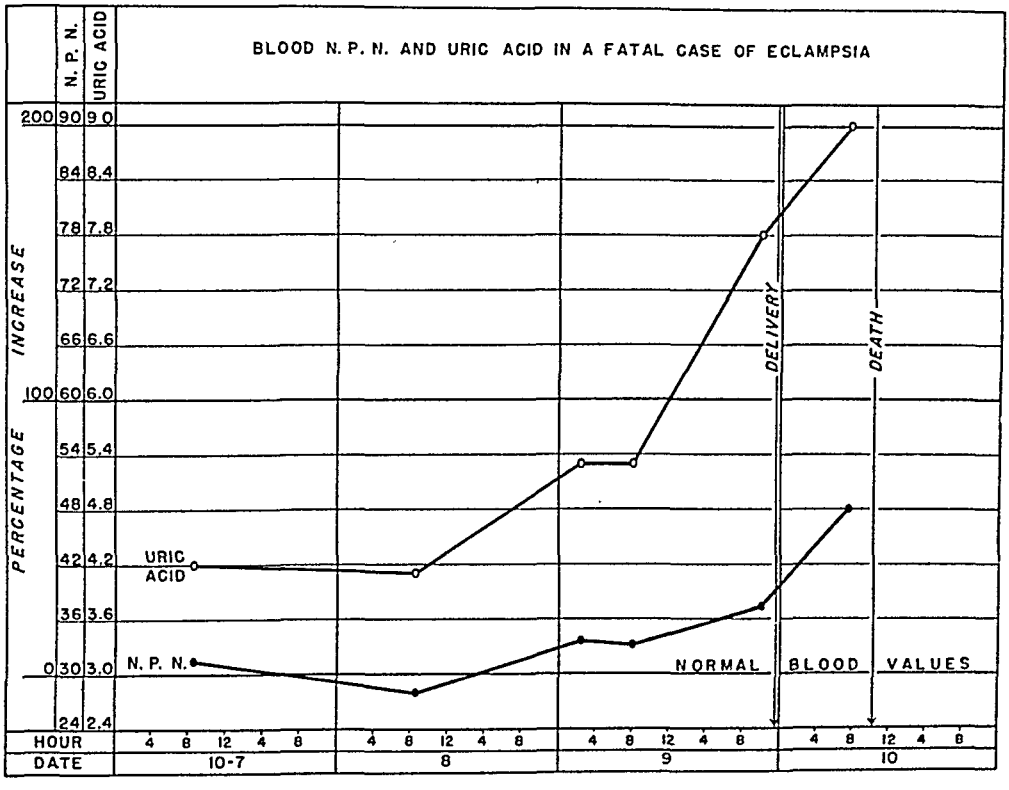


Chart 10.—Blood nonprotein nitrogen and uric acid in a fatal case of eclampsia.

disease, whereas kidney manifestations, such as nitrogenous retention as shown by the nonprotein nitrogen and urea values, appear late, if at all, in the course of the disease. There can be no doubt regarding the existence, in some fatal cases, of a typical "kidney of eclampsia," as described by Bell. However, all patients dying from eclampsia do not show these typical kidney lesions, which is further evidence that the kidney plays no etiologic role in the production of eclampsia. From the autopsy examination of the patient referred to above, whose nonprotein nitrogen and uric acid values are shown in Chart 10, it would seem wholly improbable that the kidneys played any role, not only in the etiology of the disease, but also in her death.

What then is the cause of the elevated uric acid in the blood of the eclamptic patient? An exogenous source seems definitely ruled out,

when we bear in mind that the eclamptic patient is usually taking no food by mouth during the time of the acute illness, a period during which the blood uric acid may be steadily rising.

We have referred to factors which decrease uric acid elimination. These include certain aromatic acids, ketosis and high lactic acid concentrations. Eclampsia, as shown by Stander and Radelet,[13] is associated with increased blood lactic acid, but if this elevation affects mainly the kidney excretion of uric acid, as Quick found, our results would indicate that an increased blood lactic acid is probably not the factor producing high blood uric acid in eclampsia.

If we assume, as indicated above, that from 30 to 50 or 70 per cent of the uric acid formed in the body is destroyed in the liver, it is a logical supposition that in eclampsia this destruction of uric acid may be interfered with. Should this be the case, the increased blood uric acid in the face of normal kidney excretion of this substance, becomes understandable. Mann and his co-workers found that in dogs, with complete extirpation of the liver, there is a marked accumulation of uric acid due, they believe, to the abolition of uricolysis. We must, however, be careful in the interpretation of these animal experiments, when considering uric acid metabolism in the human, being, for the reason that in the dog, unlike in man, there is normally almost complete uricolysis, and only traces of uric acid can be found in the blood stream. Nevertheless, Mann's work gives indirect support to the theory of decreased uric acid destruction in the liver where this organ is diseased or involved, as in eclampsia or chloroform poisoning. It is interesting to note that in a fatal case of acute yellow atrophy with marked impairment of deaminization, Rabinowitz found a normal blood uric acid value. Is it possible that here uric acid formation, as well as its destruction, was greatly reduced?

SUMMARY

A study of 5 cases of eclampsia shows that this disease is not associated with decreased excretion of uric acid and that the high blood uric acid, which invariably accompanies the disease, is probably due to impaired destruction of this substance in the liver. This impairment in hepatic destruction of uric acid appears early in the disease and may perhaps be of assistance in our search for the etiology of eclampsia. In any event, it appears as additional evidence that eclampsia is the outcome of a metabolic disturbance, and probably in one or other phase of nitrogen metabolism.

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THE EFFECTS ON THE BLOOD FROM INJECTIONS OF ENDOCRINE PRINCIPLES IN THE FEMALE

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A REVIEW of the literature conveys the lack of information concerning the study of the blood changes in connection with the administration of endocrine principles in the human being. In the past, investigation has been confined to animal experimentation.

1. Hans Scheerer studied parental injections of different hormones in animals and human beings by consecutive studies of the reticulocyte count in the circulating blood per 1,000 erythrocytes, as found in a cover glass specimen after preparation with an alcohol-azure solution. The counts were made one, two, three, five, and twenty-four hours after the injection. Special attention was paid to a possible "shift to the left of the reticulocytes" which permits differentiation of true increase in erythropoieses from mere increased liberation of reticulocytes from the bone marrow into the blood stream. He refers to a rise which increases in proportion to the amount of administered hormone units as "hormone specific." Following a test of ten different extracts, only those which primarily or secondarily acted on the sympathetic system such as the thyroid, adrenals and anterior lobe of the pituitary gland, caused a true specific rise in the reticulocytes. This was believed to be produced through increase in the blood volume circulating through the bone marrow cells, or by direct action of the sympathetic nerve fibers which enter the bone along the nutritive vessels to the bone marrow cells. In all instances the reticulocytosis produced by the anterior pituitary hormone was believed to be identical with marked physiologic reticulocytosis of pregnancy.

2. Meyer, Stewart, Thewlis and Rusch call attention to the fact that it has long been known that under certain conditions of oxygen want, there regularly occur hyperplasia of the bone marrow and an increase in hemoglobin, erythrocytes, and reticulocytes in the peripheral blood. They believe that if the pituitary furnished a hormone which affected the erythrogenic tissues, the response in the hypophysectomized animals to diminution in oxygen tension of the erythrogenic tissues might be deficient in one or more respects. They found that hypophysectomy in rats invariably is followed by anemia and a significantly subnormal reticulocyte count. The stimulus of reduced oxygen tension of the tissues is not followed by reticulocytosis or bone marrow hyperplasia in hypophysectomized rats, whereas this is constant in normal animals. There is, however, increase in erythrocytes and hemoglobin under stimulation of oxygen want if the stimulus is applied within ten days after hypophysectomy, but none if the rats are exposed twenty-five days or more after operation. They believe that this discrepancy is due to a temporary persistence of some pituitary hormone, though the reticulocytes are not increased as a result of oxygen want or the administration of liver extract. They further found that the administration of antuitrin growth hormone and anterior pituitary extract (G. A. P.) which is deficient in the thyrotropic and gonadotropic substances, to hypophysectomized rats, is followed by sharp, invariable increase in the erythrocytes. The authors conclude that the pituitary probably affects erythropoieses. It is their impression that the results probably depend on a hormone action.

3. Stodtmeister studied the blood changes in hypophysectomized dogs and the effect of the pituitary extracts on the hemopoietic system. He refers to the fact that most investigators found decrease in hemoglobin and erythrocytes following hypophysectomy.

HISTORY OF INVESTIGATION

A more thorough understanding of the action of endocrine principles in the female patient was suggested by the recognition of hypochromic anemia in cases showing endocrine imbalance.

Women, commonly, never seem to maintain a normal concentration of hemoglobin and this deviation from the normal usually occurs between 25 and 45 years of age. Such variation does not seem to occur in the male.

This leads one to inquire: Why do so many imbalanced glandular cases become anemic, and why are they more numerous in women between 25 and 45 years of age?

With the knowledge of the heightened functions of the different endocrine glands concerned in the different stages of female life, and the common existence of hypochromic anemia, there should be no hesitancy in associating some interrelationship between the endocrine system and the stability of the hemopoietic system.

The endocrine system must certainly be at a disadvantage in maintaining its balance before and after the advent of menstruation, and in later years, its regulation. Finally, it may be subjected to the increased demands and insults exigeant of their functions during pregnancies.

During the recognition and treatment of the syndrome commonly referred to as menopausal in type, it was found that hypochromic anemia in varying degrees accompanied 90 per cent of the cases.

The blood picture of hypochromic anemia has shown improvement in the majority of cases by injections of liver. In my experience, these results, as a rule, are but temporary. The blood count soon returns to its former level. A second course of injections failed to give as marked response as the first, and with the same resulting recession.

Many forms of liver, iron, combinations of iron and copper, vitamins, ventriculin, hydrochloric acid, etc., were resorted to orally, with the hope of maintaining the seemingly satisfactory response from the injections of liver. Difficulty was experienced in maintaining the improved level and in a number of cases the drop in hemoglobin was lower than previous to the injections.

MATERIAL

The material comprises a thorough four-year study of 30 private patients, women of intelligence, ranging in ages from 17 to 64 years. Each was known to have a definite hypochromic anemia and syndrome of symptoms indicative of a marked glandular imbalance. In the interim, several hundred patients have been treated and the interpretation of complete blood counts is presented in Table I.

SYNDROME

The syndrome of symptoms, in the cases referred to, are a well-defined group. They represent the experience of a great many females. A number of symptoms occurring at 45 years of age are designated as menopausal for want of a better term.

While these symptoms are associated with the climacteric, it is believed they should be classed as a syndrome resulting from failure or an interruption of the normal interrelationship of the pituitary, thyroid, ovary, and adrenals. They are more definitely interpreted as a syndrome resulting from a slow and insiduous change in the glandular imbalance which takes place between adolescence and 45 years of age. Such syndrome may be present at any age and its prominence is indicative of the degree of imbalance of the functions involved.

Postoccipital headache, melancholia, discontent, marked pessimism, sobbing, depression, vertigo, and insomnia are fairly constant in the signification of this disturbance.

Hot flushes have been noted with less frequency than the above classification unless the 45-year age limit is reached and are observed as a rule when sudden ovarian failure takes place from destruction or removal of both ovaries.

Pregnancy frequently is an injurious factor relative to the efficiency of the different glands. Maternal glandular activity is so accelerated during fetal development that endocrine principles are increased to a level surpassing that formerly experienced, enabling many females to enjoy the most healthful time of their life. A variable time ensues following either the first, second or third postgestation period when a depleted function is conspicuous by the advent of the syndrome.

By taking a thorough history of each patient, one can learn when the onset of the first appearance of such syndrome occurred and subsequent to which particular pregnancy.

Furthermore, I have frequently observed the same disturbance after the removal of the entire uterus where the ovaries have been preserved.

TREATMENT

The first routine adopted, each individual received injections of progynon for six consecutive days totaling 2,250 R. U. Following this, injections of anterior pituitary-like principle (A. P. L. or antophysin) 100 R. U. twice weekly until 1,000 R. U. were given. Complete blood counts were taken previous to and following the entire course of treatment.

Considerable enthusiasm was created because a certain group of cases showed an immediate response of from 10 to 20 per cent in the improvement of the hemoglobin and a corresponding increase in the erythrocyte count.

An interesting observation followed this improvement. An effort was made to maintain the improved blood picture by resorting to the previously mentioned method of administering orally numerous forms of iron, liver and iron combinations, ventriculin, etc. In a number of cases the blood count returned to the low level which existed prior to endocrine treatment.

In the cases where the response from the endocrine administration was not maintained after oral medication, the repeating of the former endocrine principles by injection caused the hemoglobin to again return to near normal limits.

In the greater majority of patients treated, it has been necessary to repeat the course of hypodermic injections due to the return of the syndrome. It has been noted at this time that there is a corresponding recession of near 50 per cent from the former improved state of the blood. The repetition of treatment is usually advisable in four to six months. After repeating the same course of treatment, symptoms disappear for the second period lasting from seven to ten months. Further repetition of the treatment has kept a greater number of patients free from symptoms for a longer period of time, lasting from twelve to eighteen months.

TABLE I

A. EFFECTS ON HEMOGLOBIN AND ERYTHROCYTES

ESTROGEN AND PITUITARY-LIKE PRINCIPLES

*INCREASE		AGE	*DECREASE	
EST.	PIT.		EST.	PIT.
50%	73%	Under 45 years	50%	27%
62½%	83%	Above 45 years	37½%	17%

B. EFFECTS ON LEUCOCYTES

54½%	45½%	Under 45 years	45½%	54½%
25%	100%	Above 45 years	75%	0%

*The increase or decrease signifies from 10 to 20 per cent.

Following the course of injections of endocrine principles, a well-balanced combination of glands, consisting of ovary, thyroid, and anterior pituitary, is administered orally. The dosage of each ingredient is arranged suitable to the patient's requirements. Continuous and indefinite administration is insisted upon. This treatment is given with the thought that certain glandular principles of undetermined recognition would be conducive in maintaining the level of the blood improved by the injections or replacements of the endocrine principles.

The blood picture has presented a more satisfactory stabilization when orally administered glands are given after the injection of endocrine principles.

In addition to the encouraging results first noted, another phase of great interest was the recognition of certain individuals who exhibited a definite menopausal syndrome, yet experienced an entirely opposite effect on the blood picture than the ones which were benefited. These negative and seemingly detrimental effects were observed and corroborated by the lowering of the blood count. It has been perplexing to reason why two individuals, much alike physically and with a syndrome similar, experience two different extremes as indicated by the blood counts and modification of relief of the syndromal symptoms.

In an attempt to explain this intrusion of glandular interrelationship, a second routine was adopted whereby blood counts were taken previous to and following the administration of each of the two different principles. The results of this observation conveyed valuable information.

The hemoglobin and erythrocyte count was increased by progynon and decreased by anterior pituitary-like principle or antophysin in a group of cases. In another group, an opposite effect, a decrease of hemoglobin and erythrocyte count by the administration of progynon and an increase following anterior pituitary-like principle or antophysin.

The effects on the blood picture of all cases, as demonstrated by the white blood cell and neutrophile counts, are quite interesting.

Age seems an important consideration with regard to the action of estrogen and pituitary-like principles on the leucocytes. After 45 years of age, estrogen produces an antagonistic action on the leucocyte mechanism, causing a leucopenia while the pituitary principle is just as prominent in creating an increase or a leucocytosis. This action is noticeably opposite in patients previous to 45 years of age.

SUMMARY

In review of the complex and changeable results in the blood counts of a series of females showing endocrine imbalance, one is confronted with the different effects on the hemoglobin, erythrocytes, leucocytes and neutrophile counts from the injection of the different commercial endocrines.

It would seem courageous to attempt to evaluate such action and proves rather conclusively that each individual must be studied separately as to what constitutes the imbalance. This entails a com-

TABLE II. TABULATION OF EFFECTS ON THE BLOOD FROM INJECTIONS OF ESTROGEN OR ANTERIOR PITUITARY-LIKE PRINCIPLES

AGE	HEMOGLOBIN				R. B. C.				W. B. C.				NEUTROPHILE			
	INCREASE		DECREASE		INCREASE		DECREASE		INCREASE		DECREASE		INCREASE		DECREASE	
	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST.	PIT.	EST	PIT.	EST.	PIT.
Under Forty-Five Years of Age																
17		1				1						1		1		
18		1				1				1				1		
23	0	1	0			1	1		1			1	1			1
28			1		1				1				1			
29	1			1	0	0	0	0		1	1		1	1		
30	1						1		1				1			
30			1	1	0		0	1	1			1			1	1
30	1				1						1				1	
31	1	1			1	1					1	1		1	1	
33		1	1			0	1	0		1	1			1	1	
39	0	1	0		1	1					1	1		1	1	
39			1	1			1	1	1			1	1			1
42	1				1				1				1			
42		1				1				1				1		
42		1	1				1	1	0	1	0		1			0
Above Forty-Five Years of Age																
45	1				1						1				1	
47	1	1			1	1			1	1				1	1	
49		1				0		0		0		0				1
50	1				1						1		1			
54	0		0	1			1	1		1	1		1	1		
57	1				1						1		1			
58		0	1	0		1	1			1	1				1	1
63	1	1			1	1			1	1			1	1		
64		1	1			1	1			1	1				1	1

plicated determination of the percentages of endocrine principles which are to be considered normal; the percentage of endocrine principles which would be necessary at different times to equal the normal balance; an illustration of which would be the changeable amounts of principles produced during the menstrual cycle. In the administration of a principle corresponding to the least deficient, an oversupply may be produced and in some unexplainable manner, either an anti-action or obscure action might be brought about to produce an especial detrimental effect on the blood mechanism.

Seventy-six and one-half per cent of the patients were improved by the injections of the pituitary-like principle. Sixty per cent of the patients responded to estrogen favorably.

In 23.5 per cent of the patients, the percentage of hemoglobin and the erythrocyte count were decreased by the pituitary-like principle. Forty per cent of the cases were decreased by the action of estrogen.

One patient, not included in the above percentages, experienced a definite lowering of the hemoglobin and erythrocyte count from the administration of estrogen and after an interval of time, a further lowering from the administration of the pituitary-like principle. The reactions in this case were marked and caused aggravation of the syndrome.

Separate consideration is necessary so that the action of the individual patient should be the criterion for the final determination of the selection, time and amount of the endocrine principle to be administered in the treatment of endocrine imbalance.

The administration of one principle may cause a decline in the percentage of hemoglobin and the erythrocyte count, only to reverse the picture on replacing a different principle which produces a definite response higher than the initial count.

Just what effect may be produced from a possible oversupply of any one principle necessitates careful consideration. When one thinks of the toxicity attendant with the disturbed function of the thyroid gland, it seems logical to assume that any one of the other internal secreting glands may be disturbed to the point of producing detrimental effects. The lack of knowledge of the continuous variations and interruptions in the supply of the different principles in each individual creates a complicated and confusing problem.

The almost daily changeable functional supply of the different glandular principles, occurring at different periods during the monthly cycle of the female, is illustrative of what seems to create an obstacle in the determination of the amount of any principle to be administered without the possibility of producing an imbalance with injurious results in a certain proportion of endocrine cases.

The effect on the blood mechanism in a certain group of endocrine cases justifies suspicion of some obscure detrimental action in contrast to a decided beneficial effect in another group. There may be justification for assuming that the imbalance of different endocrines and hypochromic anemia are closely associated and that a specific action on the hemopoietic system does exist.

The study of repeated complete blood counts, before and after a number of injections of each principle, properly timed, offers considerable valuable information which may create more accuracy and satisfaction in the selection of the specific endocrine principle to be employed and the time and amount advisable in each individual.

CONCLUSIONS

1. A definite syndrome of symptoms is indicative of a slow and insidious failure of the glands of the endocrine system in the female and occurs at any age.

2. The endocrine system is related in some specific manner in the maintaining and stabilization of the hemoglobin and erythrocyte count of the blood.

3. Maintenance of hemoglobin and erythrocyte count often is accomplished more satisfactorily after replacement of endocrine principles.

4. Increased accuracy in the determination of the principle and dosage to be given hypodermically and the relief of syndrome is obtained by complete blood counts before and after the administration of each endocrine principle.

5. Endocrine patients should not be treated with endocrine principles unless a study of the blood is made at the same time.

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PREGNANCY COMPLICATED BY SICKLE CELL ANEMIA

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SICKLE cell anemia as a complication of pregnancy has been reported five times in the literature since the first description of the disease in 1910.[1] We wish to present two additional cases of acute sickle cell anemia in pregnancy, and to discuss some problems of diagnosis and management.

The discovery of the sickling trait was first made by Dresbach[2] in 1904, when a negro medical student submitted a sketch of his own blood during a course in histology. The acute phase of the disease was first described by Herrick[1] in 1910. The name "sickle cell anemia" was applied to the anemic phase by V. R. Mason[3] in 1922, and the term "sicklemia" used to designate the asymptomatic sickle cell trait which may be found in 7 or 8 per cent of the colored race. Over eighty articles have been published on the subject since that time. Sydenstricker,[4] literature. Sydenstricker[7] was the first to mention an instance of sickle cell anemia in pregnancy.

Yater and Mollari[8] record the details of a 25-year-old negro woman, six months pregnant, who died of the disease and was autopsied three weeks after spontaneous abortion. Death occurred during an "abdominal crisis." This was her second pregnancy, the first having terminated as a spontaneous abortion at six months. The third case was reported by Lash,[9] whose patient was a 21-year-old colored primipara at term, dying in shock six hours following cesarean section. The diagnosis was made at autopsy. Richter and others[10] mention the occurrence of a normal delivery in a 16-year-old colored primipara with sickle cell anemia, diagnosed on the tenth post-partum day. The patient apparently responded well to liver therapy. The fifth case was reported by Lewis,[11] whose patient was a 25-year-old negro woman giving a history of three spontaneous abortions. The diagnosis of sickle cell anemia was made when she was three months pregnant, and a hysterectomy and sterilization were done. Lewis feels that the disease is an indication for the termination of pregnancy.

Although the disease has been described in great detail by numerous writers,[4-6] it may be pertinent to summarize very briefly the salient features. Both sicklemia and sickle cell anemia are congenital and hereditary diseases, transmitted through either sex as a dominant Mendelian factor, and occurring almost exclusively in the negro race. The latent trait, or sicklemia, is characterized by the peculiar "oat" or "sickle" shapes assumed by the red blood cells when removed from the circulation and maintained in a sealed preparation under reduced oxygen tension. The reaction is reversible, for the cells may assume their normal shape if the preparation is oxygenated,[12] and experimental work has shown that the same reactions may take place in vivo.[13] Sicklemia is entirely symptomless, and women who have this trait frequently give normal obstetric histories.

Sickle cell anemia, on the other hand, is a less common entity, very rare in pregnancy, and characterized by hemolytic relapses and remissions, severe anemia, the sickling phenomenon often on fresh smears, and symptoms of weakness, muscular and joint pains, jaundice, and a tendency for vascular thromboses. There may be leg ulcers and acute abdominal crises, possibly due to thrombosis of abdominal vessels. Individuals with the disease are often of poor physique, succumb readily to slight infections, and rarely live past thirty years of age. There is no specific treatment. The characteristic findings at autopsy are essentially the same as those described below (Case 2). During childhood, the spleen may be greatly enlarged, but later the constant destruction of pools of sickle cells with the deposition of hemosiderin, together with infarction and fibrosis, may reduce the size of the spleen.

REPORT OF CASES

CASE 1.—Mrs. A. C., a colored primigravida, aged 19 years, entered the hospital on Sept. 15, 1935, complaining of generalized weakness and joint pains.

There were no familial diatheses. The only past illnesses had been frequent colds and "rheumatic attacks," and pneumonia. The patient was now over eight months pregnant, the last menstrual period having occurred Jan. 1, 1935. She had been attending an outpatient maternity clinic for prenatal care, and during the past month had been placed on a fat-free diet because of epigastric pain and jaundice, although there was no other evidence of gall bladder disease. She had been subject to joint pains, particularly in the knees and elbows at various intervals. During the past week she had remained in bed because of progressive weakness, jaundice, and anorexia. She reported some recent weight loss.

The significant findings on physical examination were a marked icteric tint to the skin and sclerae, with pallor of the mucous membranes. Temperature, 99.4° F.; pulse, 96; respiration, 20; blood pressure, 120/80. The tonsils were large and infected. The heart and lungs were not remarkable. The liver was enlarged, the edge being palpated two fingerbreadths below the costal margin. There was considerable epigastric tenderness. The spleen was not palpable. The height of the uterine fundus was 30 cm. above the symphysis pubis. The fetus was in left occipitoposterior position, and the fetal heart tones were regular, with a rate of 130. All pelvic measurements were within normal limits. No peripheral edema was noted.

The urine was deeply bile stained; specific gravity, 1.018, sugar and acetone, negative; 0.6 gm. albumin per liter. Microscopic examination showed a few pus cells, but no red blood cells or casts. The initial blood count showed 40 per cent hemoglobin and 1,800,000 red blood cells. The white cell count was 11,000, with 87 per cent neutrophiles. Sedimentation time, 18 mm. fall in twenty-five minutes. Blood Wassermann and Kahn negative.

The clinical impressions on entry were (1) primigravida, three weeks from term, not in labor; (2) probable toxic hepatitis, either due to early acute yellow atrophy or catarrhal jaundice; and (3) moderately severe anemia, unexplained.

About twelve hours after admission she was re-examined with identical findings. It was felt at this time, in view of her race, the anemia, and the history of joint pains and jaundice, that sickle cell anemia should be considered; hence a complete hemogram and studies of blood chemistry were requested.

The laboratory reports were as follows: Hemoglobin, 42 per cent (Sahli); erythrocytes, 1,660,000; color index, 1.30; leucocytes, 18,850, with 72 per cent neutrophiles, 25 per cent lymphocytes, and 3 per cent monocytes. Marked anisocytosis and poikilocytosis, with marked polychromasia. There was some basophilic stippling and many Jolly bodies. Normoblasts 66 per 100 leucocytes. There was marked sickling of the red cells. Reticulocyte count was 23 per cent. Fragility test, initial hemolysis at 0.28; hemolysis not complete at 0.24. Hanging drop showed marked sickling of the red blood cells after eighteen hours.

Blood Chemistry.—Nonprotein nitrogen, 22 mg. per cent; urea nitrogen, 9.5 mg. per cent; uric acid, 4.2 mg. per cent; carbon dioxide combining power, 48 volumes per cent; van den Bergh test gave a prompt positive direct reaction, and an indirect quantitative bilirubin of 20 mg. per cent. Blood cholesterol, 200 mg. per cent; icterus index, 250 units.

On the basis of these findings the diagnosis was revised to pregnancy complicated by sickle cell anemia, and the patient was started on a high caloric liver diet, with reduced iron and copper medication.

During her six weeks' stay in the hospital, 7 transfusions, each of 500 c.c. of blood, were given both by the direct and the indirect citrate methods. On October

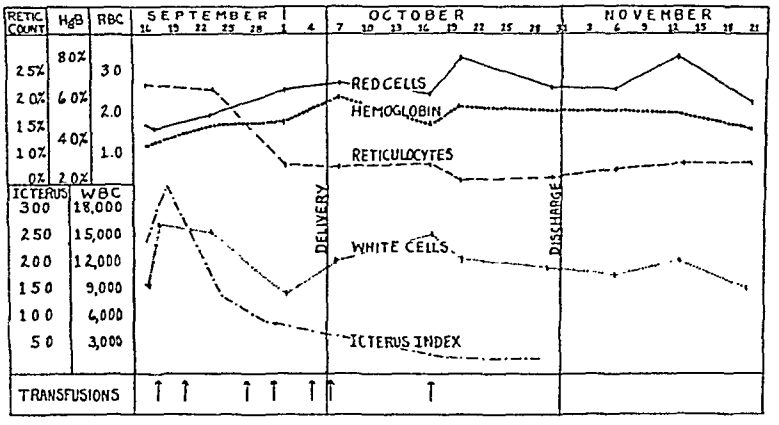


Fig. 1.—Chart showing hematologic findings (Case 1).

20, 3 capsules of Lextron (Lilly) three times a day were substituted for the reduced iron and copper; otherwise there was no alteration of treatment. Eleven hemograms and repeated chemical examinations of the blood were made at regular intervals. To conserve space, the hemograms are presented in graphic form in Fig. 1. With the exception of the van den Bergh tests and icterus index, the remaining chemical determinations did not vary significantly from the values given above. The direct van den Bergh showed a prompt positive response in seven determinations, although the jaundice was probably of a hemolytic type. The bilirubin value fell gradually from 20 mg. per cent to 2.2 mg. per cent. The icteric index, as shown in Fig. 1, was 250 units on admission, rose to 350 units on the third day after admission, then gradually fell to 40 units over a period of six weeks.

During the first week there was marked improvement in the patient's general condition, and all symptoms subsided. There appeared to be no indications for induction of labor. On October 6 (the estimated date due), labor began spontaneously, and after a first stage of only three hours, there was a normal spontaneous delivery of a living, 6 pound 11 ounce male infant. Episiotomy was not done and vaginal examinations were eliminated in order to avoid all chance of potential infection. The measured blood loss was 150 c.c. A sealed wet mount of blood from the umbilical cord demonstrated no sickling of the red blood cells after twelve hours.

The patient's father, sister, and two half-brothers were examined for sicklemia and all were negative. The mother, however, showed definite sickling of the red blood cells in the sealed hanging drop, but none on the fresh smear. The baby was re-examined after one month and no sicklemia was found.

During the puerperium the patient remained in good clinical condition and became ambulatory on the sixteenth post-partum day. The highest temperature recorded following delivery was 99.2° F., excluding one rise from a transfusion reaction on the eleventh post-partum day. X-ray plates of her legs, arms, and skull showed no abnormalities of bony structures. She was discharged from the hospital on October 31, at which time a physical examination revealed no unusual findings.

Five follow-up examinations were made, the last on May 26, 1936 (seven months post partum). At no time were there any complaints referable to the anemia. The hemoglobin varied between 48 and 54 per cent, and the red cell count between 2.0 and 2.35 million. The baby remained in good condition.

CASE 2.—Mrs. L. S., a colored female, aged 20 years, entered the hospital at 6:00 P.M. on April 22, 1935, complaining of pains in the chest.

Her general health had been good until the onset of the present illness. She was subject to frequent colds, but none had been serious. There was no history of joint pains, anemia or jaundice. Both her mother and father were living and well. There had been no previous pregnancies.

The last normal menstrual period began on Nov. 22, 1934, and she stated that she was now five months pregnant, and had felt life for three weeks. About four weeks ago she caught a "cold" which confined her to bed, and was characterized by cough, weakness, and malaise. These symptoms persisted until five days ago, when she noticed chest pains, chilly sensations, difficulty in breathing, nausea and vomiting, and a hacking cough. Two days ago she began to spit up blood-tinged mucus. The symptoms became gradually worse until entry to the hospital.

The physical examination revealed a fairly-well developed, colored female appearing to be acutely ill. There was a distinct icteric tinge to the sclerae, and rapid and labored breathing. The rectal temperature was 101° F., pulse 160, and respirations 36. Blood pressure, 115/70. The tongue was dry and coated. The anterior cervical glands were enlarged, but not tender. The heart did not appear to be enlarged; the sounds were rapid, but regular and without murmurs. There were areas of dullness at both bases, with bronchial breath sounds, suggestive of bilateral consolidation. The abdomen was distended, but soft, and there was a symmetrical soft mass rising to the level of the umbilicus. Fetal heart tones could not be heard. There was tenderness in both flanks, especially on the right. The pelvic findings were consistent with a five and a half to six months' pregnancy, the size of the uterus appearing to be larger than the duration of amenorrhea would indicate.

Examination of the blood revealed 35 per cent hemoglobin; red blood cell count, 1,920,000; color index, 0.92; white cell count, 47,800, with 87.5 per cent neutrophiles, 3.0 per cent lymphocytes, 9.0 per cent monocytes, and 0.5 per cent myelocytes. The platelets appeared normal. There was marked anisocytosis, and poikilocytosis, with some polychromasia. There were 5 nucleated red blood cells for each 100 leucocytes. Examination of fresh mount for sickling phenomenon was not done.

There were no significant findings in the urine.

The clinical impressions were: (1) bilateral bronchopneumonia; (2) five and one-half to six months' pregnancy; (3) possible macrocytic primary anemia of pregnancy (in view of color index of 0.92), undetermined type; and (4) unexplained jaundice.

There was a rapid downhill course, with death occurring twenty-two hours after admission.

Autopsy was performed by Dr. L. J. Tragerman, who has kindly submitted the following summary of the essential pathologic findings:

Autopsy was performed nineteen hours after death. The body was that of a well-developed and nourished colored female. No abnormalities were noted in the cranial cavity. Heart weighed 420 gm.; the valves and myocardium appeared normal throughout. The chambers of the heart as well as many of the blood vessels throughout the body, particularly the pulmonary arteries, inferior vena cava, portal system, pelvic veins and many of the major aortic branches were

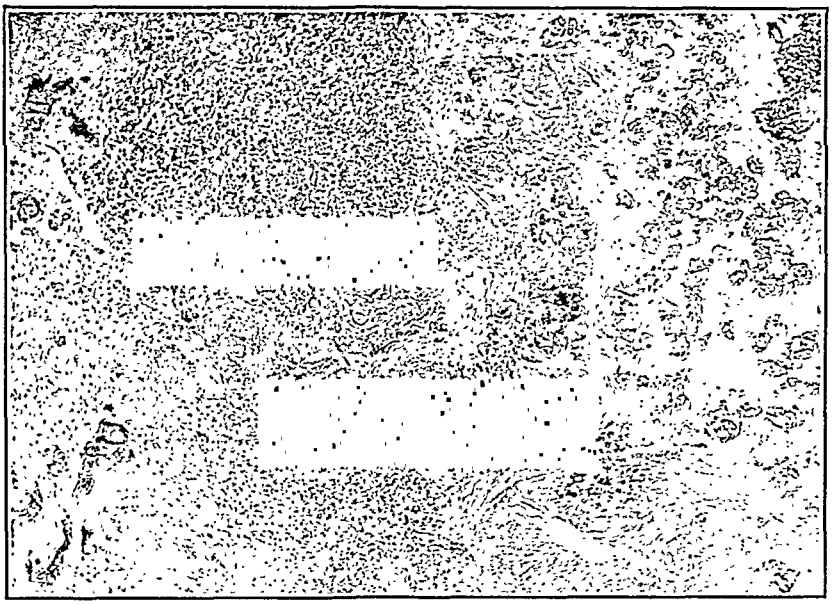


Fig. 2.—Photomicrograph of spleen. Note extreme siderofibrosis and pools of blood. (×95.)



Fig. 3.—Section of placenta (×645) showing sickling of cells in maternal blood sinus. Note sickle cells in capillaries.

partially filled with a stringy, loose, red-brown clot, appearing recently ante mortem. The right lung weighed 660 gm.; upper lobe appeared normal and middle and lower lobes contained numerous hemorrhagic infarcts, varying up to 2 cm. in maximum diameter. In many of the branches of the lower lobe there was present firm, gray-pink thrombotic material. Left lung weighed 670 gm. The upper lobe appeared normal. The lower lobe contained numerous small hemorrhagic infarcts similar to those present in the right lower lobe. The peritoneal cavity, gastrointestinal tract, liver, pancreas, and adrenals were essentially normal. The spleen was unusually small, measuring about 3 cm. in its broadest capsular surface,

and weighed close to 20 gm. Capsule was smooth and mottled purple gray, and was slightly thicker than normal. Surfaces made by section were firmer than normal and of variegated green-gray and pink-brown color with completely obscured Malpighian markings. Kidneys together weighed 490 gm. and were of equal size and similar gross appearance. Capsule stripped with some difficulty from a dull brown surface and the cut surface markings were obscure. Kidney pelves and ureters were moderately dilated. The lower urinary tract was normal. Cervix was closed, soft and smooth. The body of the uterus was enlarged, consistent with pregnancy, and its cavity contained a normally attached placenta, amniotic sacs and well-developed twin fetuses, each about 20 cm. in length.

The only abnormality in the adnexal structures was the presence of numerous firm, gray-brown to red thrombi, not adherent to the walls of the veins in the broad ligament. The bone marrow in the lower end of the femur and in the tibia was bright red.

Histologic examination confirmed the presence of hemorrhagic infarcts in the lungs, with an associated early bronchopneumonia and revealed the presence of deformed erythrocytes, many of them typically sickled, in virtually all the maternal blood vessels examined. Ante-mortem thrombi were seen in the pelvic veins with sickle cells packed into the margins of the thrombi. The spleen (Fig. 2) showed the most striking alteration in histologic appearance. The capsule was thickened by a dense fibrous tissue in which some infiltration with iron pigment was present. Pulp sinusoids were distended with packed, distorted erythrocytes, all showing some degree of sickling. In addition there were scattered perifollicular hemorrhages. Many areas were almost completely avascular, showing a severe degree of siderofibrosis with hyalinization and thickening of both the Malpighian corpuscles and trabeculae, and deposition of large quantities of pigment material confirmed by special stain to contain iron. Liver showed cloudy swelling, slight iron pigmentation and numerous sickle cells in the sinusoids. In the kidney the glomerular tufts were made prominent by clumps of sickle cells. Cloudy swelling of the tubular epithelium was present. Impression smear of the tibial marrow (Wright stain) showed moderate hyperplasia, predominantly of erythrogenetic elements.

The veins in the uterine wall showed many sickle cells as did the maternal vessels in the placenta (Fig. 3). Capillaries seen in the chorionic villi showed normal erythrocytes. Sections of the fetal organs of both the male and female fetuses showed no deformity of erythrocytes beyond that usually seen in formalin fixed tissue. There were hematopoietic foci in the liver with normally-shaped erythrocytes. The umbilical vein of the female fetus showed a few deformed erythrocytes on section, but no definite sickled cells.

Anatomic Diagnosis.—(1) Sickle cell anemia; (2) thrombophlebitis, pelvic veins; (3) embolism, pulmonary arteries, with multiple infarcts; (4) pregnancy, twins, five months; and (5) siderofibrosis, spleen, severe.

DISCUSSION

Of the seven cases now reported where pregnancy occurred with sickle cell anemia, 3 patients died and only two progressed to an uneventful delivery. While the course of pregnancy and delivery may be entirely normal from an obstetrical standpoint, gestation does appear to exert an unfavorable influence upon women with the disease. In fact, the reduced alkali reserve and reduced oxygenation of blood which may accompany pregnancy, and which favor the sickling phenomenon experimentally[12, 13] may be factors in the production of the acute phase, although this is entirely hypothetical. If the patient improves with repeated blood transfusions and the usual antianemic measures, she may be successfully carried to term. Extraordinary precautions should be taken to avoid infections at the time of delivery, and to conserve blood.

It is difficult to explain the tendency to the thromboses, which directly led to death in our second patient. Diggs[6] believes that the abnormal shape of the red blood cells may act mechanically to block the vessels. Possibly the congestion of pelvic vessels accompanying the pregnancy was an additional factor. The

multiple infarcts of the lungs, apparently embolic from the pelvic veins, led to a clinical diagnosis of bronchopneumonia. In the first case, the jaundice, severe anemia, and joint pains in a negro woman led to the diagnosis of sickle cell anemia, confirmed by blood studies. The diagnosis of sickle cell anemia is easily made, once it is suspected.

SUMMARY

Two cases of sickle cell anemia complicating pregnancy are presented and discussed. It is most likely that pregnancy is a factor in producing an exacerbation of the disease. The multiple thromboses which are often characteristic of the disease proved fatal in the second case. With proper supervision it is possible, however, to carry pregnancy successfully to term in spite of severe sickle cell anemia.

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STUDIES ON PREGNANDIOL*

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PREGNANDIOL is the only known excretion product of the corpus luteum hormone, progesterone, in the urine. In this study the pregnandiol content of the urine was determined in 5 cases in which the menstrual history was normal, in 50 cases in which biopsy was performed on the endometrium of nongravid women who presented gynecologic complaints, in 10 cases of early gestation, in one case during the last month of gestation, and in 51 cases during the first week post partum. With the exception of the 5 normal nongravid women, all of these patients were seen in the Section on Obstetrics and Gynecology at the Mayo Clinic.

HISTORY OF PREGNANDIOL

Marrian, in 1929, made extracts from the urine of pregnant women for further chemical study of estrogenic compounds and obtained a physiologically inactive solid alcohol which he did not identify. Butenandt, in 1930, had also observed this inactive substance and, after the accumulation of nearly 2 gm. of the material from the residues remaining from the extraction of estrone from more than 1000 liters of

*Abridgment of thesis submitted by Dr. Wilson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Obstetrics and Gynecology.

Submitted for publication May, 3, 1938.

urine of gravid women, was able to identify it. He named it "pregnandiol" because it was thought to occur only in the urine of pregnancy. The formula which Butenandt gave pregnandiol is $C_{21}H_{36}O_2$. The structural formula as proved by him is given in Fig. 1, *A*. Progesterone, the hormone of the corpus luteum, has the formula $C_{21}H_{30}O_2$[3]; its structural formula is shown in Fig. 1, *B*.

From a comparison of these two formulas, it is seen that the unsaturated diketone, progesterone, differs but little from the saturated alcohol, pregnandiol. Butenandt and Schmidt, in 1934, having noted this structural similarity, were able to produce pure progesterone from pregnandiol by a method of pseudosynthesis. By oxidizing pregnandiol obtained from the urine of pregnant women, they obtained a saturated diketone which was brominated and this product was treated with pyridine to effect the elimination of hydrogen bromide. The unsaturated diketone thus obtained was identical with the corpus luteum hormone, progesterone. The physiologic potency of progesterone obtained in this manner from pregnandiol has been proved by Selye and his collaborators in some of their work on the relationship between progesterone and estrin. Odell and Marrian made a further contribution when they found an acid-hydrolyzable form of pregnandiol in the alcohol-washed butyl alcohol extract obtained from the urine of pregnant women. Venning and Browne, in 1936, presented a gravimetric method of extracting the water-soluble complex, sodium pregnandiol glucuronate, from the urine of pregnant women. In 1937, Venning, Henry,

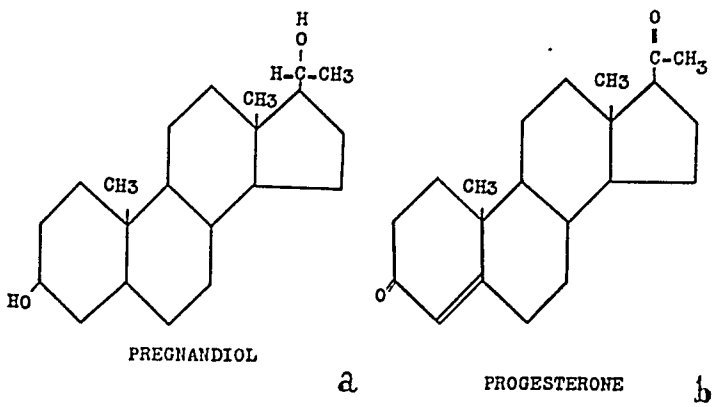


Fig. 1.—*a*, Pregnandiol; *b*, progesterone.

and Browne found this same complex in the urine of nongravid women and stated that it was present in significant amounts only during the luteal phase of the menstrual cycle. Because they found the substance excreted in increasing amounts throughout pregnancy, because of the close time relationship between the formation of the corpus luteum and the appearance of the complex in the urine during the menstrual cycle, and because intramuscular injection of progesterone was followed by the excretion of sodium pregnandiol glucuronate in the urine, they concluded that this last named compound was an actual excretion product of progesterone. There may be other compounds of progesterone excreted in the urine but pregnandiol is the only form now identified.

In the light of these findings, this relationship between the amount of pregnandiol in the urine and that of progesterone produced by the corpus luteum would seem to mean that the amount of pregnandiol in the urine would be an index to the function of the corpus luteum. It seems logical, therefore, to consider the determination of the pregnandiol content of the urine as a method for determining the function of the corpus luteum.

METHOD OF EXTRACTION

The butyl alcohol extraction method of Venning has been used in this study to determine the pregnandiol content of the urine. The butyl alcohol extract, obtained by this method, is evaporated to dryness and the residue is dissolved in 1/10 N

sodium hydroxide, which is then re-extracted with butyl alcohol and again evaporated to dryness. The residue is then dissolved in water and the sodium pregnandiol glucuronate in solution is precipitated two times with acetone. The precipitate obtained is dissolved in ethyl alcohol and, after the alcohol is evaporated, the residue, sodium pregnandiol glucuronate, is weighed.

The complex extracted directly from the urine is a monosodium salt of pregnandiol glucuronic acid. The formula for this salt is $C_{27}H_{43}O_8$-NaH_2O. It contains one molecule of water of crystallization and has a molecular weight of 536. Since the molecular weight of pregnandiol is 320, the factor for conversion of sodium pregnandiol glucuronate into terms of pregnandiol is 320/536 or 0.597. The values stated in this paper are in terms of pregnandiol.

In the determination of the pregnandiol content of the urine after the method of Venning, considerable care is exercised in the removal of impurities by dissolving the residue in water and precipitating the sodium pregnandiol glucuronate with acetone; this is followed by centrifugation and filtration. There may be, however, a small amount of impurity present in the final product which varies directly with the amount of urine extracted and inversely with the amount of pregnandiol present; for example, a relatively small volume of urine containing a relatively large amount of pregnandiol will yield a nearly pure product, whereas a large volume of urine containing a small amount of pregnandiol will give a product which is for the most part impure. In cases in which the final weight of the sodium pregnandiol glucuronate is of the order of 0.5 mg. or less, we consider that the residue consists mainly of extraneous substances and that the amount of sodium pregnandiol glucuronate is negligible.

OTHER METHODS OF EVALUATING CORPUS LUTEUM FUNCTION

Until the aforementioned method for estimating the amount of pregnandiol in the urine was developed, the principal measure of function of the corpus luteum was the microscopic appearance of differentiative changes in the endometrium. Infertility, menorrhagia, metrorrhagia, a shortened interval between the menstrual periods, repeated abortions, and perhaps dysmenorrhea, often suggested a deficient or absent function of the corpus luteum. It is not within the scope of this paper, however, to discuss the differences of opinion in regard to the etiology, terminology, and significance of the changes that may occur in the endometrium as a result of disturbance in normal hormonal stimulation. The terminology of Herrell and Broders has been employed to classify normal and abnormal endometriums: The terms "early" and "late proliferation" are given by them to the early and late effect of estrin on the endometrium in the first half of the menstrual cycle (Fig. 2). "Early" and "late differentiation" are the terms they applied to the early and late effect of progesterone on the endometrium in the luteal phase or last half of the menstrual cycle (Fig. 3).

The microscopic findings in the endometrium that seem to indicate disturbance of the progesterone effect are degrees of failure of development of differentiation. The differentiative phase in the endometrium is often designated as the "secretory phase." Cystic degeneration is often associated with this evidence of failure and, in its most marked form, has been called "cystic glandular hyperplasia." Failure of progesterone to stimulate the endometrium normally results in degrees of lack of differentiation that often seem to be in proportion to the symptoms that the patient presents. By microscopic study of these endo-

metriums, one of us[7] has shown that cystic changes can occur in all phases of the menstrual cycle. Thus, cystic changes in a differentiated endometrium probably are the first microscopic evidence of functional failure of the corpus luteum (Fig. 4). Complete absence of differentiation, with persistence of proliferation with or without cystic change

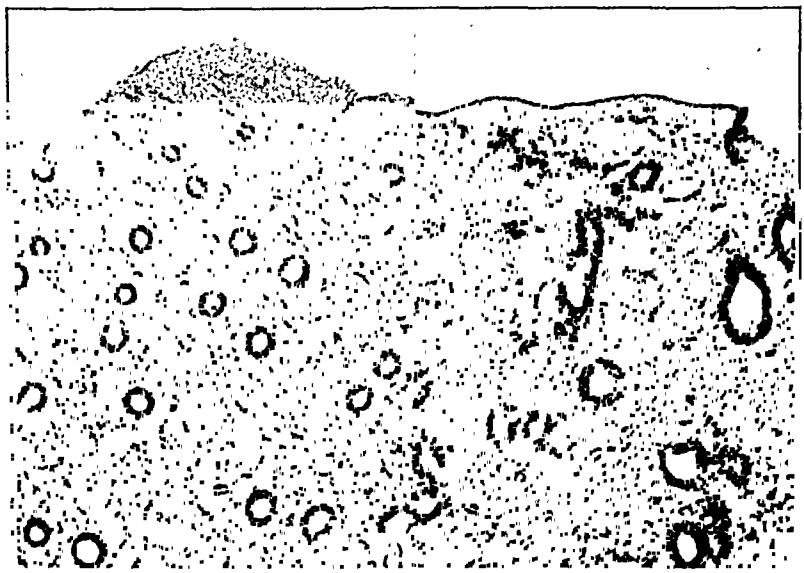


Fig. 2.—*A* (Case 1, Table I.), Early proliferative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50); B (Case 4, Table I.), late proliferative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50).

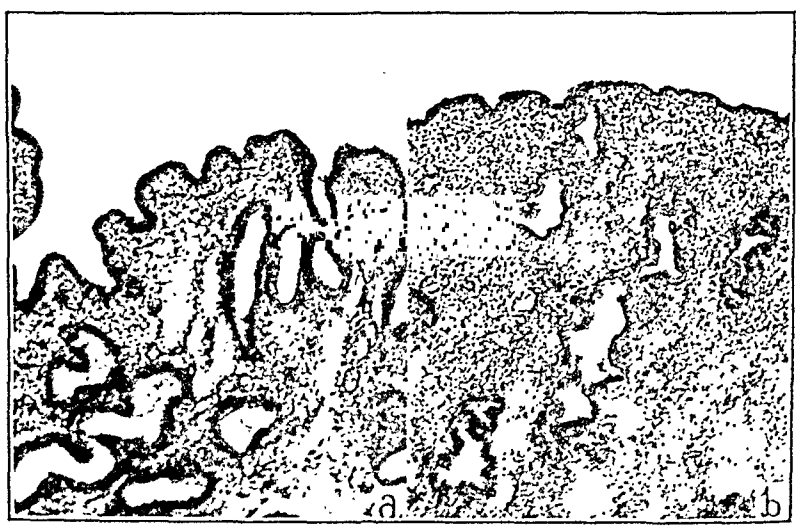


Fig. 3.—*A* (Case 10, Table I.), Early differentiative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50); *B* (Case 17, Table I.), late differentiative phase of the menstrual cycle in a normal endometrium (hematoxylin and eosin, ×50).

(Figs. 5 and 6, *A*), apparently is associated with complete absence of function of the corpus luteum, although it indicates that estrogenic stimulation is still present. When this state exists, the diagnosis of persistent proliferation of the endometrium is made. Complete failure of the ovary to produce estrin naturally results in atrophy of the endometrium (Fig. 6, *B*). This series of cases in which endometrial biopsy

was performed did not happen to reveal an endometrium in the stage of early proliferation in association with cystic change. A slide of endometrial tissue showing this type of microscopic change was therefore borrowed from the Section on Surgical Pathology in order to make the series of photomicrographs more representative (Fig. 5, *A*).



Fig. 4.—*A* (Case 49, Table III.), Early differentiative phase of the menstrual cycle in an endometrium with cystic changes Grade 2 (hematoxylin and eosin, ×50); *B* (Case 44, Table III.), late differentiative phase of the menstrual cycle in an endometrium with cystic changes of Grade 4 (hematoxylin and eosin, ×50).

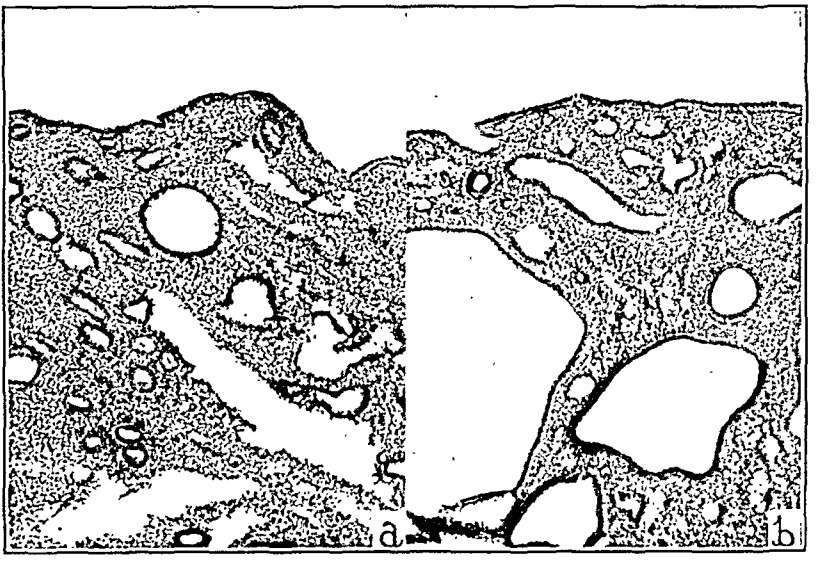


Fig. 5.—*A*, Early proliferative phase of the menstrual cycle in an endometrium with cystic changes of Grade 2 (hematoxylin and eosin, ×50); *B* (Case 27, Table II.), late proliferative phase of the menstrual cycle in an endometrium with cystic changes of Grade 4 (hematoxylin and eosin, ×50).

NORMAL VALUES FOR PREGNANDIOL IN THE URINE

No great amount of data is as yet available in regard to the amounts of pregnandiol to be found in the urine of nongravid women with normal genital function. Venning and Browne[12] presented the results of

pregnandiol determinations in 10 cases in which the menstrual history was normal. These determinations were not controlled by microscopic study of the endometrium. The basis for acceptance of Venning's values as normal is therefore the menstrual history. It is a well-known fact, however, that the menstrual history is often inaccurate. Furthermore, cases are often encountered in which cyclic uterine bleeding occurs from an undifferentiated endometrium, bleeding indistinguishable clinically from normal menstruation. Values for pregnandiol obtained in cases in which the only basis for normalcy is the occurrence of uterine bleeding at regular intervals therefore may be open to question. Thus in the cases reported by Venning, pregnandiol was found only for a period of three days in the luteal phase in one case and, in other cases, it was present for a period of twelve days. On the days of the luteal phase of the menstrual cycle when pregnandiol was found in the urine of all of Venning's patients the values varied from 1 to 7.2 mg. in twenty-four hours.



Fig. 6.—*A* (Case 24, Table II.), Early and late proliferative phases of the menstrual cycle in an endometrium with cystic changes of Grade 2 (hematoxylin and eosin, ×50); *B* (Case 22, Table II.), atrophic endometrium (hematoxylin and eosin, ×110).

Perhaps microscopic study would have revealed abnormal endometriums in some of these cases.

For these reasons it is not possible to state definitely the range of normal excretion of pregnandiol and such data as are available at this time are merely indicated. Fig. 7, *A* is a composite curve for the excretion of pregnandiol which has been constructed by us from the values reported by Venning. Fig. 7, *B* represents the same type of curve for a group of apparently normal women whose excretion of pregnandiol was measured by us.

In the human subject it is customary to consider the menstrual cycle as extending from the first day of a period to the first day of the succeeding period. It will be noted in Fig. 7 that the luteal phase of the menstrual cycles was found by counting back from a menstrual period rather than by counting forward from the first day of the preceding menstrual period. This was done for the reason that, if a menstrual period has

occurred in a normal individual, more definite dates can be assigned to the luteal phase than if the time of the luteal phase is based on the occurrence of an anticipated menstrual period. Repeated microscopic studies of the endometrium of several hundred normal women during the luteal phase of the menstrual cycle will have to be studied, together with the results of repeated estimations of pregnandiol for the same

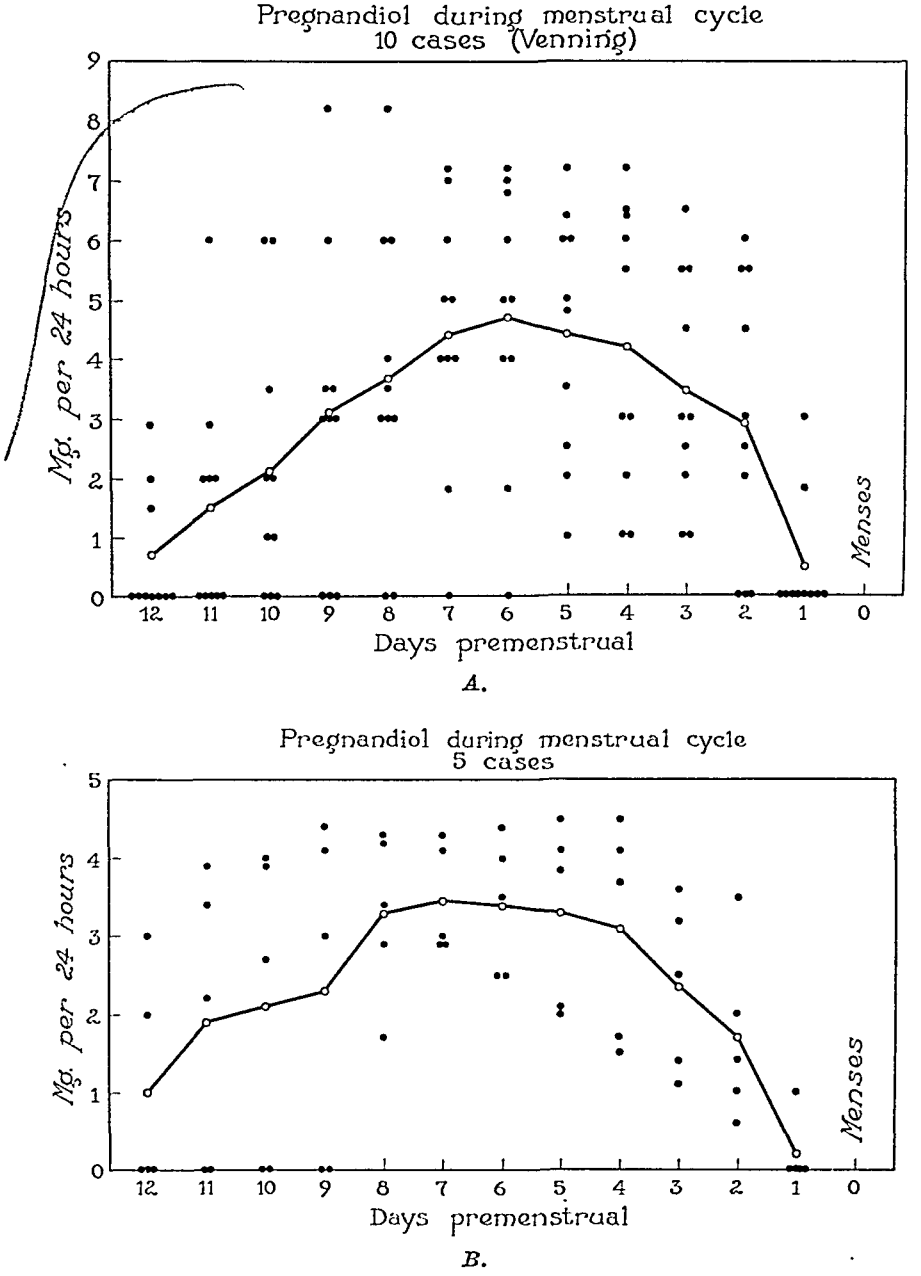


Fig. 7.—Excretion of pregnandiol: *A*, Graph constructed from Venning's report; *B*, graph constructed from our observations.

patients, in order to solve the problem of normal values. Until such a time as this can be accomplished, the values given in Fig. 7 will have to suffice as the criteria of normal excretion of pregnandiol in the urine.

The estimations thus far made by us of the amounts of pregnandiol in the urine of presumably normal women during the luteal phase of the menstrual cycle correspond to those of Venning.

RESULTS

I. Cases in Which Pregnandiol Was Estimated and in Which Endometrial Biopsy Was Performed.—The data which were obtained from an investigation of the 50 cases in which endometrial biopsy was performed are shown in Tables I, II and III. Table I reveals the amounts of pregnandiol present in cases in which the endometrium was normal microscopically. It is to be emphasized that these patients presented

TABLE I. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED A NORMAL MICROSCOPIC APPEARANCE OF THE ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
1*	No cycle	1.28	Early proliferative	Scanty flow every few days for past year
2	15 after 13 before	0.557	Early proliferative	Infertility, scanty menses. Nonpatent tubes
3	20 after ? before	0.51	Late proliferative	Sterility and obesity. Past 2 years menses irregular and scanty. Last interval 3 mo.
4*	10 after 18 before	0.342	Late proliferative	Infertility. Dysmenorrhea. Flow lasts from 5 to 14 days
5	11 after 17 before	0.55	Late proliferative	Infertility. Tubes patent. Basal metabolic rate -13 and -15
6	13 after 22 before	1.48	Late proliferative	Infertility
7	21 after 0-8 before	0.855	Late proliferative	Secondary infertility. Tubes patent. Obesity
8	19 after 11-21 before	0.34	Late proliferative	Infertility. Menstrual interval 30-40 days, flow 9 days. Tubes patent. Husband negative. Basal metabolic rate -21 and -10
9	17 after 11 before	2.9	Early differentiative	Menorrhagia, 1 year. Serologic tests for syphilis, 4+
10*	20 after 3-9 before	9.85	Early differentiative	Infertility. Husband sterile
11	22 after 6 before	0.342	Early differentiative	Infertility. Previous right tubal pregnancy. Tubes nonpatent
12	25 after 3 before	5.9	Late differentiative	Mild dysmenorrhea. Urinary prolan: 20 R.U./liter; urinary estrin: 40 + R.U./liter; (12th day of cycle)
13	24 after 4 before	0.457	Late differentiative	Infertility. Basal metabolic rate low for 7 years
14	24 after 3 before	5.6	Late differentiative	Infertility, 3 years. Menorrhagia, 5 years. Basal metabolic rate -12
15	24 after 4-6 before	0.6	Late differentiative	Infertility, 7 years. Tubes patent. Basal metabolic rate -4
16	28 after 0-1 before	0.26	Late differentiative	Infertility. Basal metabolic rate -12
17*	23 after 5 before	0.3	Late differentiative	Secondary infertility. Very scanty menses, lasting only 2 days. Basal metabolic rate 0. Tubes nonpatent to inflation and iodized oil

*Photomicrographs of the endometriums in these cases shown in Figs. 2 and 3.

histories of the complaints previously mentioned which are considered to be evidence of disturbance in normal genital function even though microscopic examination of the endometriums revealed no abnormality. Significant amounts of pregnandiol were present in two (Cases 1 and 6) of the 8 cases in which the endometrium was in the proliferative phase. Case 1 was one of metrorrhagia in which persistent proliferation existed. In Case 6, the significant amount of pregnandiol was found in conjunction with the late proliferative phase.

In the remaining 9 cases in this table, the endometrium was in a stage of differentiation. In 4 of these 9 cases amounts of pregnandiol were present which might be considered as normal in light of the values obtained in cases in which the menstrual cycle is normal. Failure to find normal amounts of pregnandiol in conjunction with the microscopically normal endometriums in the other five cases demands some explanation. In Case 16, it is to be noted that the determination of pregnandiol and the biopsy were made the day before the onset of the menstrual

TABLE II. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED AN ABNORMAL PROLIFERATED ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
18	60 after ? before	1.11	Late proliferative, Grade 2, cystic	Metrorrhagia, 3 months. Infertility, husband sterile. Obesity. Basal metabolic rate +1
19	No cycle	0.0	Late proliferative, Grade 2, cystic	Metrorrhagia, 1 to 6 napkins required daily for past 4 years
20	24 after 4 before	0.42	Late proliferative, Grade 2, cystic	Age 40, "normal" menses, 5 normal pregnancies. No gynecologic complaints
21	20 after 2-15 before	1.28	Late proliferative, Grade 1, cystic	Habitual abortion. Irregular cycle, interval 22 to 35 days
22*	No cycle	0.426	Atrophic endometrium	Nervousness, nausea, vomiting, relieved by menstruation, 4 years' amenorrhea, age 16 to 20, now age 26. Periods now about every 4 months. Basal metabolic rate -22. Urinary estrin: +10 R.U./24 hours. Prolan: 0
23	14 after 3 before	0.486	Late proliferative, Grade 2, cystic	Migraine. Short 17-day cycle with 7-day flow. Basal metabolic rate -7
24*	20 after 12 before	0.342	Early and late proliferative, Grade 2, cystic	7 abortions from 1921 to 1937. Obesity and headaches. Basal metabolic rate +9
25	15 after 13 before	0.298	Late proliferative, Grade 2, cystic	Infertility, 2 years. Appendicitis and peritonitis 6 years ago. Tubes patent. Husband: 0. Basal metabolic rate -11 and -8
26	No cycle	0.47	Late proliferative, Grade 1, cystic	Menometrorrhagia, otitis media. Basal metabolic rate +52, +39, +47, +30
27*	No cycle	0.94	Late proliferative, Grade 4, cystic	Menometrorrhagia
28	No cycle	1.71	Late proliferative, Grade 2, cystic	Menometrorrhagia

*Photomicrographs of the endometriums in these cases are shown in Figs. 5 and 6.

TABLE III. CASES IN WHICH PREGNANDIOL WAS DETERMINED AND IN WHICH ENDOMETRIAL BIOPSY REVEALED AN ABNORMAL DIFFERENTIATED ENDOMETRIUM

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
29	27 after 2 before	1.11	Late differentiative, Grade 3, cystic	Infertility, 5 years. Spontaneous abortion 7 years ago
30	17 after 9 before	1.79	Early differentiative, Grade 2, cystic	Sterility, obesity, arthritis. Basal metabolic rate +1
31	25 after 3 before	0.597	Early differentiative, Grade 3, cystic	Two episodes of vaginal spotting
32	20 after 8 before	2.8	Early differentiative, Grade 2, cystic	Infertility, 4 years. Husband: -0. Tubes patent
33	19 after 8 before	3.8	Early and late differentiative	Infertility. Tubes patent. Basal metabolic rate +3. Urinary prolan: 0 Estrin: 21 R.U./24 hr.
34	19 after 11 before	5.0	Early differentiative, Grade 2, cystic	Infertility. Tubes patent. Basal metabolic rate -17, -8
35	22 after 2 before	0.254	Late differentiative, Grade 1, cystic	Secondary infertility, 1½ years. Has one child age 3. Basal metabolic rate -2
36	34 after ? before	0.076	Late proliferative and early differentiative	Regular menses until 1 year ago. Since every 42 to 49 days, scanty. Hirsutism, obesity, dysmenorrhea. Basal metabolic rate -2. Urinary estrin: 20 R.U./24 hr.
37	24 after 6-11 before	2.9	Late differentiative, Grade 4, cystic	Infertility. Tubes nonpatent to 200 mm. Hg.
38	16 after 14 before	0.85	Early differentiative, Grade 1, cystic	Occasional vaginal spotting. Infertility. Chronic mastitis. Basal metabolic rate: 0
39	24 after 4 before	2.39	Late differentiative, Grade 2, cystic	Infertility, 3 years. Mittelschmerz. Tubes patent. Basal metabolic rate -16, -25, -22
40	20 after 6 before	0.5	Late differentiative, Grade 2, cystic	Infertility, 4 years. Tubes patent. Husband had reduced number sperm. Basal metabolic rate -4
41	23 after 5 before	4.0	Early and late differentiative, Grade 2, cystic	Recurrent pyelonephritis, colon bacilluria, trichomonas, sterility (husband sterile). Basal metabolic rate -9
42	21 after 7 before	0.34	Late differentiative, Grade 2, cystic	Infertility. Tubes patent. Basal metabolic rate -11
43	22 after 6 before	1.37	Late differentiative, Grade 1, cystic	Infertility, 7 years. Husband: 0. Tubes patent
44*	27 after 2 before	1.62	Late differentiative, Grade 4, cystic	Dysmenorrhea. Trichomonas. Basal metabolic rate -11, -8

*Photomicrographs of the endometriums in these cases are shown in Fig. 4.

TABLE III—CONT'D

CASE	DAYS BEFORE AND AFTER ONSET OF MENSES	AMOUNT OF PREGNANDIOL PER 24 HR., MG.	REPORT OF ENDOMETRIAL BIOPSY, PHASE	COMPLAINTS AND OTHER DATA
45	24 after 4 before	1.78	Late differentiative, Grade 2, cystic and polypoid	Secondary infertility. 2 normal preg., 6 and 7 years ago. Tubes patent. Basal metabolic rate -7
46	22 after 6 before	0.256	Late differentiative, Grade 1, cystic	Mild dysmenorrhea
47	18 after 10 before	0.65	Late differentiative, Grade 2, cystic	Infertility, 6 years. Tubes patent. Husband: 0. Basal metabolic rate +11
48	25 after 3 before	1.2	Late differentiative, Grade 1, cystic	Trichomonas. Chronic cystic mastitis
49*	18 after 3 before	0.513	Early differentiative, Grade 2, cystic	Oligomenorrhea. Secondary infertility 4 yr. Tubes patent. Basal metabolic rate +15, +21, +18, -11
50	21 after ? before	0.94	Early differentiative, Grade 1, cystic	Menorrhagia, irregular interval, infertility. Tubes patent. Basal metabolic rate +2

*Photomicrographs of the endometriums in these cases are shown in Fig. 4.

flow. In the present state of our knowledge, it is considered that the amount of progesterone secreted by the corpus luteum is markedly less just before the onset of menstruation, therefore one would expect pregnandiol to be absent or to be present in only minimal amounts in the urine at this stage of the cycle. In the other cases of this type, it is entirely possible that the determinations were made too close to the time of the menstrual period because of an inaccurate menstrual history; it is quite common for a woman to be inaccurate, to the extent of four or five days, in giving her menstrual history. It may be that these cases might have shown a normal excretion of pregnandiol had the opportunity for several estimations been available. During the course of this investigation, it has become increasingly evident that the amounts of progesterone (as evidenced by the excretion of pregnandiol in the urine) which are necessary to differentiate the endometrium in a given case may vary considerably. For example, in the 5 cases under discussion, in which low values for pregnandiol were associated with a normally differentiated endometrium, it may be that these endometriums differentiated in response to a minimal amount of progesterone.

This theory of endometrial response, while in no way conclusive, may have some practical significance. Here are 5 cases in which the endometrium was normal microscopically and yet infertility and scanty menses were complained of. Heretofore, these cases might have been considered normal from the hormonal standpoint, but this low finding of urinary pregnandiol may indicate that there is a deficiency of the corpus luteum in this type of case.

Table II shows the amounts of pregnandiol present in 11 cases in which, with one exception, the endometrium was in a stage of proliferation. In this one exception (Case 22), microscopic examination revealed an atrophic endometrium. In 8 of these cases minimal amounts of pregnandiol were present, which is the expected finding during the proliferative phase; however, it is significant that in Cases 18, 21, and 28, more than 1 mg. of pregnandiol was found in a twenty-four-hour specimen of urine. It is to be noted that this finding occurred in association with the late proliferative phase. In six of these 11 cases (Cases 18, 19, 23, 26, 27, and 28), the fact that the patients bled from a proliferated endometrium would indicate a

persistence of proliferation and probably a complete or nearly complete failure of the corpus luteum. Case 20 is of interest because it is illustrative of the findings in women approaching the menopause, and it also illustrates the fact that cyclic uterine bleeding can occur from a proliferated endometrium.

The data obtained in the remaining 22 of the 50 cases in this group are given in Table III. In these cases, the endometrium was in a stage of differentiation. In 12 of these 22 cases, significant amounts of pregnandiol were found in the urine, and, in 3 (Cases 33, 34 and 41) of these 12, amounts of pregnandiol were present which were in the upper normal range.

It is evident, from the data presented in Table III, that in only 3 of these 22 cases were normal or maximal amounts of pregnandiol found. It is to be noted that in 20 of the 22 cases in this table a significant amount of cystic change was found in the differentiated endometrium; this indicates to us that these were not normal endometriums.

It was possible to make repeated estimations of the urinary pregnandiol in Cases 34 and 35, during a considerable part of the menstrual cycle. The data collected in these two cases again emphasize the value of repeated estimations of pregnandiol. The amounts of pregnandiol per twenty-four hours and the time in the cycle during which these amounts were obtained is shown in Table IV. Both of these patients had regular menstrual cycles and a flow which did not vary from normal in amount or duration. In Case 34, menstruation occurred every thirty days and lasted five days; in Case 35, menstruation occurred every twenty-four days and lasted three days. From the standpoint of the menstrual history these patients might well be considered as normal, and such cases as these might occur in any group such as those studied by Venning and by us for normal excretion of pregnandiol. Because of the cystic changes in the endometrium which were evident microscopically, however, it would seem that these patients were not normal. This, therefore, serves again to emphasize the statement previously made that the menstrual history is not necessarily an accurate criterion of normalcy. If endometrial biopsy had not been performed in these two cases, Case 34 might well have been considered normal because the amounts of pregnandiol that were excreted in the urine were in the range of normal values. On the other hand, Case 35 would have been considered abnormal because of the small amounts of urinary pregnandiol that were found. Examination of the endometrium revealed that Case 34, which had the greatest corpus luteum function as evidenced by urinary pregnandiol, showed a more marked

TABLE IV. AMOUNT OF PREGNANDIOL PER TWENTY-FOUR HOURS

AMOUNT OF PRENANDIOL PER 24 HR., MG.	DATE IN CYCLE
Case 34 (30-Day Cycle)	
0.8	11
0.51	13
2.6	14
6.2	15
4.0	16
3.2	18
5.0	19*
Case 35 (24-Day Cycle)	
0.597	15
0.51	16
0.68	17
0.43	18
0.21	19
2.6	20
0.254	22†
0.34	23
0.34	24

*Biopsy revealed early differentiation, Grade 2 cystic endometrium.
†Biopsy revealed late differentiation, Grade 1 cystic endometrium.

degree of cystic change in the endometrium than did Case 35 in which a higher degree of cystic change would have been expected. It would seem that a logical explanation for these findings, as has been previously indicated, is that the endometrium must be considered as a definite entity and that the endometrial response to progesterone is a variable factor.

It may ultimately be shown that normal hormonal function is more dependent on the relation between the amounts of estrogenic hormone and progesterone than upon the actual amounts of either. It is well known that the corpus luteum does produce estrogenic hormone as well as progesterone. It is logical to infer that the estrogenic hormone secreted by the corpus luteum is essential to the development and function of the endometrium during the luteal phase of the menstrual cycle.

It seems evident, therefore, from the data in these two cases, that an evaluation of the function of the corpus luteum is much more accurate when several determinations of pregnandiol can be made and that normal values for pregnandiol and a normal menstrual history may be entirely misleading unless endometrial biopsy is performed.

II. Estimation of Pregnandiol in the Urine of Gravid Women.—The data obtained from estimations of pregnandiol in 10 cases during early gestation are shown in Table V. In all these cases the history was of normal, regular menstruation, one or two periods had been missed, and pregnancy was then later proved to be present. It is evident that pregnandiol was excreted in the urine in all of these cases either in normal amounts or in amounts in excess of those found during the luteal phase of the menstrual cycle. The data on urinary pregnandiol during gestation are incomplete, but the amounts found during the later months of gestation are considerably

TABLE V. CASES IN WHICH DETERMINATIONS OF PREGNANDIOL WERE MADE DURING EARLY GESTATION

CASE 2	DURATION OF GESTATION	AMOUNT OF PREGNANDIOL PER 24 HR., MG.
1	2 months	5.9
2	8½ weeks	14.4
3	6½ weeks	9.0
4	7 weeks	5.1
5	2 months	8.3
6	2 months	6.5
7	7½ weeks	10.11
8	3 months	4.7
9	6 weeks	4.9
10	2½ months	12.2

TABLE VI. RESULTS OF PREGNANDIOL DETERMINATIONS MADE DURING LAST MONTHS OF A NORMAL GESTATION

NUMBER OF DAYS BEFORE DELIVERY	AMOUNT OF PREGNANDIOL PER 24 HR., MG.
30	53.9
28	31.2
26	50.5
24	51.0
22	27.3
19	35.6
17	53.1
15	55.8
12	73.5
10	56.8
7	47.0
4	71.6
2	43.2

higher, varying between 27 and 75 mg. per twenty-four hours. Table VI shows the results obtained in one case in which pregnandiol estimations were made during the last month of normal gestation.

III. Estimation of Pregnandiol on the Fourth Day Post Partum.—The data obtained on estimating pregnandiol in 51 cases on the fourth day post partum are shown in Fig. 8. It is evident that in 45 and 21 per cent of these cases pregnandiol was excreted in negative and minimal amounts, respectively. In 16 per cent the urinary pregnandiol had a mean value of 2.75 mg. per twenty-four hours; in 18 per cent the mean value was 6.0 mg. per twenty-four hours.

COMMENT

It seems apparent from the data so far available that there is a considerable variation in the amount of pregnandiol excreted by women with a normal menstrual history, as well as a variation in the duration of excretion during the luteal phase of the menstrual cycle. The values obtained by Venning and by us for pregnandiol in the urine of women with a normal menstrual history are essentially the same.

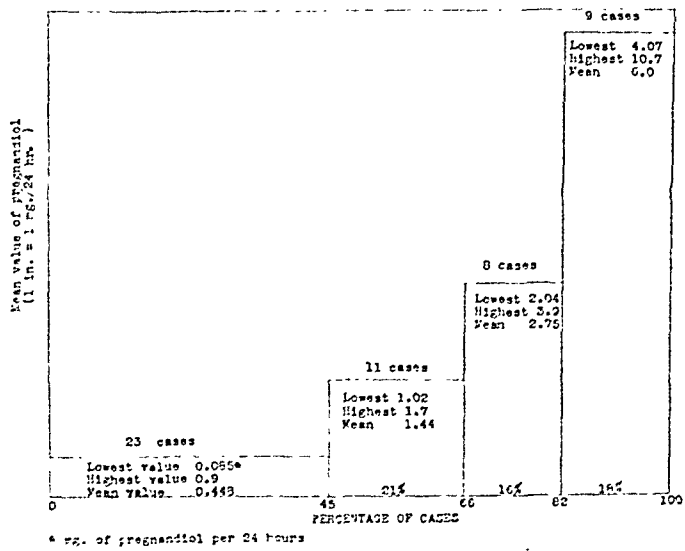


Fig. 8.—Excretion of pregnandiol on the fourth day post partum.

As is indicated in Tables I and II, significant amounts of pregnandiol have been found in the urine when a stage of proliferation existed in the endometrium. So far this has occurred, with but one exception, in association with the late proliferative phase of the endometrium. In this one exception persistent proliferation was present. This may be explained by the fact that there probably is an interval between the initial secretion of progesterone and the appearance of differentiation in the endometrium. It may be that in persistent proliferation of the endometrium some corpus luteum function is present, but not in a degree sufficient to cause endometrial differentiation. As Zondek has intimated, it may also be true that minimal amounts of progesterone continue to be produced by the corpus luteum of the preceding menstrual cycle.

The data obtained from studies carried out during the stage of endometrial differentiation, in which cystic changes were evident microscopically in 20 of 22 cases, reveal that definitely normal levels of preg-

nandiol were not present in the urine in 19 of the 22 cases. This would seem to mean that the low values obtained for pregnandiol indicated that normal function of the corpus luteum did not exist in these cases. It would seem logical, therefore, inasmuch as cystic changes have occurred in association with these low levels, that this finding can also be interpreted as evidence of insufficient function of the corpus luteum.

Low levels for pregnandiol occurred in five of the nine cases in Table I in which the endometriums were in the stage of differentiation and revealed no microscopic abnormality but in which some clinical abnormality was noted. This finding, and some of the findings in association with cystic degeneration during the stage of endometrial differentiation such as in Cases 33, 34, and 41 in Table III, would seem to indicate that the endometrial response to progesterone may vary considerably in different individuals. Furthermore these findings would seem to indicate that there may be some disturbance in the estrin-progesterone relationship. In addition, it seems evident that too much reliance should not be placed on the menstrual history as given by the patient, and it would also appear that a normal or abnormal excretion of pregnandiol in association with a normal menstrual history is not sufficient to evaluate accurately the hormonal status of any particular individual.

The data obtained from estimations of pregnandiol during early gestation would seem to mean that either normal amounts of urinary pregnandiol or amounts above normal in the case of a woman who has missed a menstrual period and whose menses have previously been regular is indicative of pregnancy. High amounts of urinary pregnandiol, such as were found in Cases 2, 7, and 10 in Table V, would seem definitely to indicate the presence of pregnancy. The excretion of pregnandiol in the remainder of these cases in amounts equal to or in excess of the upper limit of normal for pregnandiol excretion during the luteal phase of the menstrual cycle would seem to indicate pregnancy only if the fact of a missed menstrual period could be ascertained. In the last month of a normal gestation the amounts of pregnandiol in the urine in one case were found to be much greater and represented the highest excretion of pregnandiol so far observed by us.

As is indicated in Fig. 8, pregnandiol does not immediately disappear from the urine following parturition in a definite percentage of the cases, although the amount of urinary pregnandiol is much less than that found prior to parturition. This would seem to mean that there is some corpus luteum function after delivery. Whether or not this function is associated with lactation or some reparative process is not as yet known.

SUMMARY AND CONCLUSIONS

We have employed Venning's method for determining the amounts of pregnandiol in the urine, and in a group of cases comparable to those represented in her report the results of the test were essentially the same.

Pregnandiol was found in significant amounts in the urine during the luteal phase of the menstrual cycle in a majority of the cases studied.

Significant amounts of pregnandiol in the urine have been found during the stage of estrogenic activity when late proliferation existed in the endometrium.

An abnormal microscopic appearance of the differentiated endometrium is nearly always associated with low values for urinary pregnandiol. The endometrial response to apparently normal hormonal stimulation may vary.

Significant corpus luteum function, as evidenced by the amount of pregnandiol found in the urine, seems to be present on the fourth day post partum in about 50 per cent of the cases studied.

The excretion of pregnandiol in normal or maximal amounts in the urine of a woman who has missed a period and who has had a normal menstrual history is apparently indicative of early gestation.

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Kehrer, E.: Mongolism, Monatschr. f. Geburtsh. u. Gynäk. 108: 125, 1938.

The author reports four cases of Mongolian idiocy and one rare case of familial Mongolism in which a father, his illegitimate sister and two daughters showed this disease. The cerebral disturbances associated with this abnormality may be so obvious at birth that a diagnosis can easily be made. The characteristic symptoms are the facial appearance, muscular hypotonicity, extremely lax skin in the back of the neck, tendency to remain inactive, drowsiness, and shortness and inward curvatures of the end phalanges of the five fingers.

Endocrine disturbances usually manifest themselves in the first few years of life but may be observed at birth. It is usually believed that Mongolian idiots appear in women after 40 years of age but only one of the author's four mothers was over 40.

The ultimate cause of Mongolism is to be sought partly in injury to the germ plasm (ovum or sperm) and partly to damage to the embryo early in its development.

J. P. GREENHILL.

X-RAY DEMONSTRATION OF SUBMUCOUS MYOMAS BY COMBINED USE OF HIPPURAN AND CO_2 INJECTION*

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INTRAUTERINE injection of radio-opaque solutions for the specific purpose of demonstrating submucous myomas began with collargol in 1914.† Since then other forms of colloidal silver and halogen salts have been employed. These have eventually been supplanted by iodized oils and at present lipiodol is most commonly preferred.

Two techniques are in vogue. One is the fractional and the other the evacuation method. The first consists of introducing 2 c.c. of lipiodol and making the x-ray exposure. This is followed by 4 or 5 successive films each after 4, 6, 8, and 10 c.c. have been introduced into the uterine cavity. The second method consists of filming the filled uterus at its maximum capacity and again as soon as the lipiodol has been evacuated.

Each of these methods gives telltale pictures in a certain percentage of cases, visualizing submucous myomas and other growths which protrude into the uterine cavity. Both have the disadvantage of allowing the oil to pass through the Fallopian tubes and of entering the peritoneal cavity. This drawback may to a certain extent be avoided by controlling the injection with the fluoroscope. The injection is discontinued the moment the uterine cavity is seen to be filled or the oil is seen entering the tubes. The fractional method necessitates multiple exposures which must be considered in relation to the examiner and the patient.

I have sought to avoid the escape into the peritoneal cavity by introducing into the uterus a thin rubber balloon (condom or Penrose tubing), coated with lipiodol on its outer and inner surfaces. Air injected into the balloon served as contrast. Unfortunately the inflated balloon does not adapt itself to the configuration of the uterine cavity, being limited largely by its molded form. Another device which I tried was to introduce a gelatin capsule containing ether after the lipiodol was evacuated, the expanding ether vapor liberated from the dissolved capsule serving to distend the uterine cavity. Neither of these methods has been found satisfactory. The introduction of a foreign body in addition to the lipiodol is not practical, occasioning, as it does, added trauma. Although the diagnosis of submucous myomas is important in selected cases, the method employed must be considered in relation to its safety, feasibility and simplicity.

*These illustrations were demonstrated at the scientific exhibit at the meeting of the American Gynecological Society, at Asheville, N. C., May 30, 1938.

In this work I had the valuable assistance of my Resident, Dr. Arthur H. Davids, who made the routine injections.

†Röntgendiagnostik der Uterustumoren mit Hilfe von intrauterinen Collargolinjektionen, Zentralbl. f. Gynäk., No. 18, 1914.

These conditions appear to be met by adopting the group of organic iodides such as uroselectan, skiodan, diodrast and hippuran, which have been utilized in excretory urography. They have the virtue of rapid absorption. They are nonirritant and are well tolerated by the blood stream. Their elimination by the kidneys is rapid and unaccompanied or followed by harmful lesions.

For intrauterine use the amount of the organic iodide employed is not enough as a rule to visualize the urinary tract. The solution may, however, when the Fallopian tubes are freely patent enter the peritoneal cavity from which it is rapidly resorbed and soon appears in the kidney pelves, ureters, and bladder. As this occurs well after the uterographs have been obtained, they offer no confusion.

Of the substances mentioned, hippuran has so far been used for our present purposes although it is quite possible that the others may yield equally good results. It is available in crystalline powder and can be made up into 100 per cent solution, in which state it can be kept at a moderately warm temperature. When cooled it crystallizes, requiring heating before the injection. In this saturation it remains a clear solution for a half hour or somewhat longer. Weaker solutions were first used and although shadowgraphs were obtained they were not as satisfactory as the 100 per cent solution (1 gm. of hippuran to 1 c.c. of distilled water).

The hippuran is introduced into the uterine cavity by means of a 20 c.c. syringe and uterine cannula, both of which are kept warm. An x-ray exposure is made at the point when the uterine cavity is filled. As a rule, from 5 to 10 or 15 c.c. are needed in fibromyomatous uteri under pressures varying between 40 mm. Hg and 150 mm. Hg.

After the x-ray exposure is made the hippuran is withdrawn into the syringe and the cannula is removed. It is well to allow two or three minutes for the uterus to empty itself. The solution is aspirated and whatever amount remains is expelled. Another syringe filled with 20 c.c. CO_2 is now attached to a clean cannula, 1 or 2 c.c. being discharged into sterile fluid in order to displace the air contained in the uterine cannula. The cannula is introduced into the uterine cavity and the CO_2 is injected until a sense of resistance is reached which is similar to that experienced during the injection of hippuran. At this point an x-ray exposure is made. (A bullet forceps grasps the anterior cervix lip and the cannula is introduced so that its tip is just above the internal os, the rubber or metal acorn engaging the external os to prevent regurgitation.)

A manometer, indispensable when lipiodol is used, is not required with hippuran. I have first insufflated the uterus with CO_2 in order to determine the initial pressure rise necessary to force the CO_2 through the uterotubal junction, using this pressure as a guide in injecting the solution. The latter was also injected by the graduated force of the CO_2 delivered from an insufflation apparatus both for the practical control of the pressure as well as to observe differences in pressure between

the fluid and CO_2. In this maneuver it is only necessary to hold the graduated glass tube containing the radio-opaque fluid above the level of the body.

It was found that the pressures reached by the aqueous solutions exceeded to some extent those reached by the CO_2. These were not as great as when lipiodol was used. Hence the manometer was found dispensable and in the last injections we have resorted to manual injection of hippuran depending upon the filling sensation imparted to the hand.

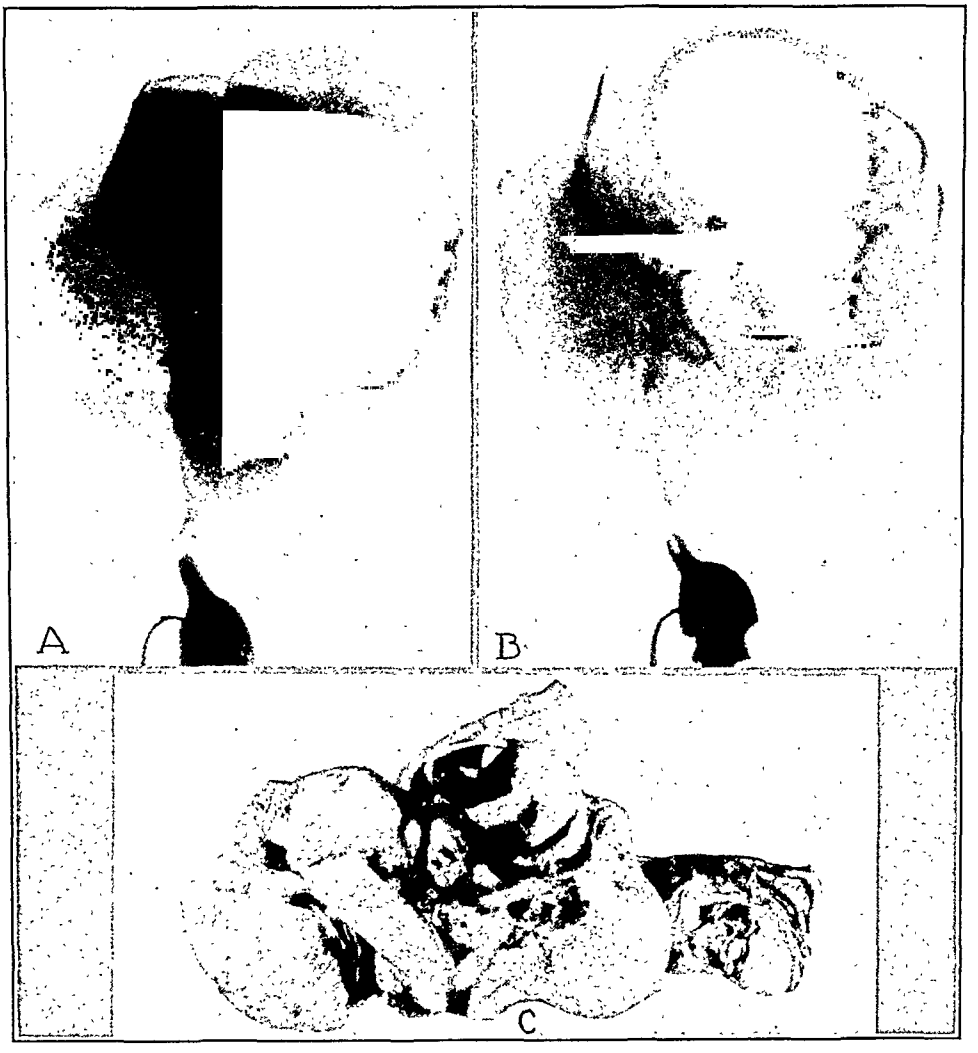


Fig. 1.—Case E. C. *A*, Hippuran hysterogram of specimen showing an irregular dilated cavity. No definite diagnosis of submucous fibroid can be made from this hysterogram. *B*, Hysteroaerogram with CO_2 injected after hippuran shows multiple submucous tumors as seen in the specimen, Fig. 1, *C*. *C*, Uterus cut open showing multiple submucous myomas visualized in Fig. 1, *B*.

RESULTS

The hippuran shadow by itself may not present the slightest indication of an intrauterine tumor. This may be seen in Fig. 1, *A*, Case E. C., where the hippuran hysterogram of the specimen showed an irregular cavity, the outline of submucous myomas definitely appearing in the hysterogram following the intrauterine injection of CO_2 (Fig. 1, *B*).

In Fig. 2, *A*, Case B. H., a single submucous myoma was not diagnosable by the hippuran hysterogram. It was beautifully outlined in the CO_2 contrast film (Fig. 2, *B*).

The same negative finding was seen in Fig. 3, *A*, Case M. M., where neither in the clinical hysterogram, by using hippuran 100 per cent nor in the specimen was a diagnosis possible of a submucous myoma (Fig. 3, *B*). The outline of the submucous tumor showed up definitely in the clinical hysterogram after CO_2 (Fig. 3, *B*), and it was also demonstrable in the specimen by the aid of CO_2 (Fig. 3, *D*).

Fig. 4, *A*, Case I. G., presents an irregular shadow with the hippuran, whereas the contrast afforded by CO_2 shows definite protrusion into the uterine cavity (Fig. 4, *B*). Uterus opened up showing the submucous myoma, *C*.

Fig. 5, *A*, Case S. K., shows no special deviation from the normal triangular shape of the uterine cavity by hippuran, whereas the submucous nature of the tumor is shown in the hysterogram with CO_2 (Fig. 5, *B*).

When a crescentic shadow is obtained by the hippuran alone, it is strongly presumptive evidence of a submucous myoma (Fig. 6, *A*). In such cases the contrast

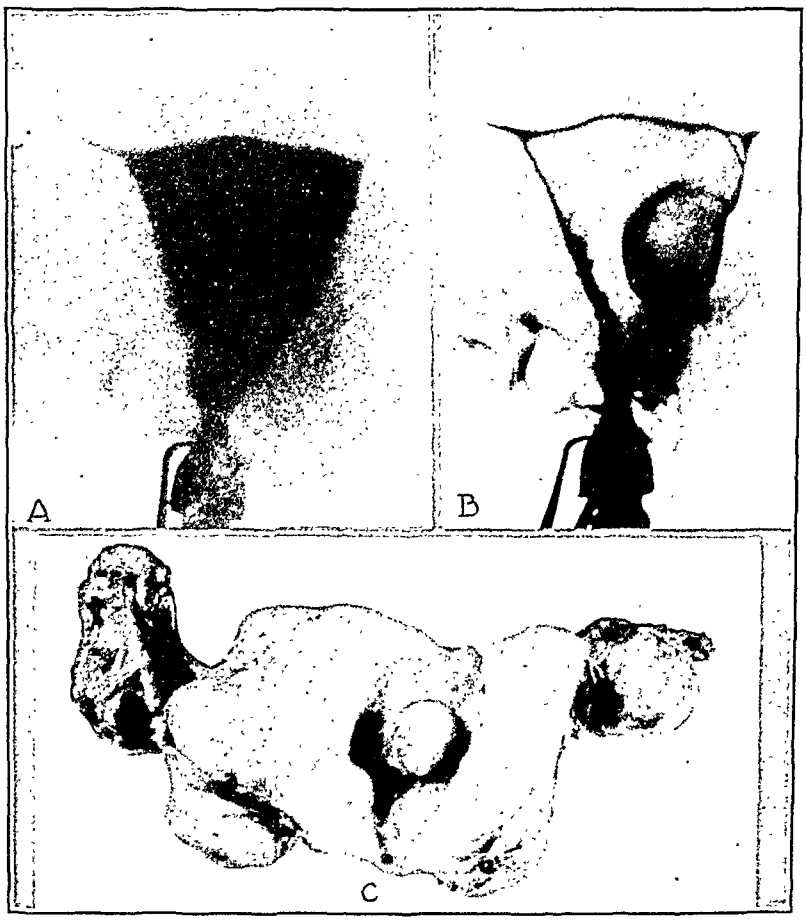


Fig. 2.—Case B. H. *A*, Hysterogram with hippuran 100 per cent solution shows a dilated uterine cavity but *no marked suggestion of the presence of a submucous* myoma. *B*, Hysteroaerogram with CO_2 injected after hippuran shows a solitary submucous fibroid which may be seen in Fig. 2, *C*. *C*, Uterus cut open showing a solitary submucous fibroid visualized in Fig. 2, *B*.

given by the CO_2 hysterogram is particularly striking, as can be seen in Fig. 6, *B*, Case P. B. In this case the submucous myoma was removed by abdominal myomectomy after which the hysterogram, Fig. 6, *C*, showed the return to the more or less triangular configuration of the uterine cavity (Fig. 6, *E*) and is prettily demonstrated in the CO_2 hysterogram, Fig. 6, *E*. Another illustration of the return to the triangular shape of the uterine cavity after a myomectomy is seen in Figs. 10, *A*, 10, *B*, 10, *C*, and 10, *D* (Case F. W.).

Fig. 7, *A*, Case C. S., illustrates a submucous myoma in the process of being extruded. The hysterogram with hippuran is not characteristic whereas the CO_2 hysterogram shows the lower pole of the tumor protruding into the cavity of the uterus near the internal os.

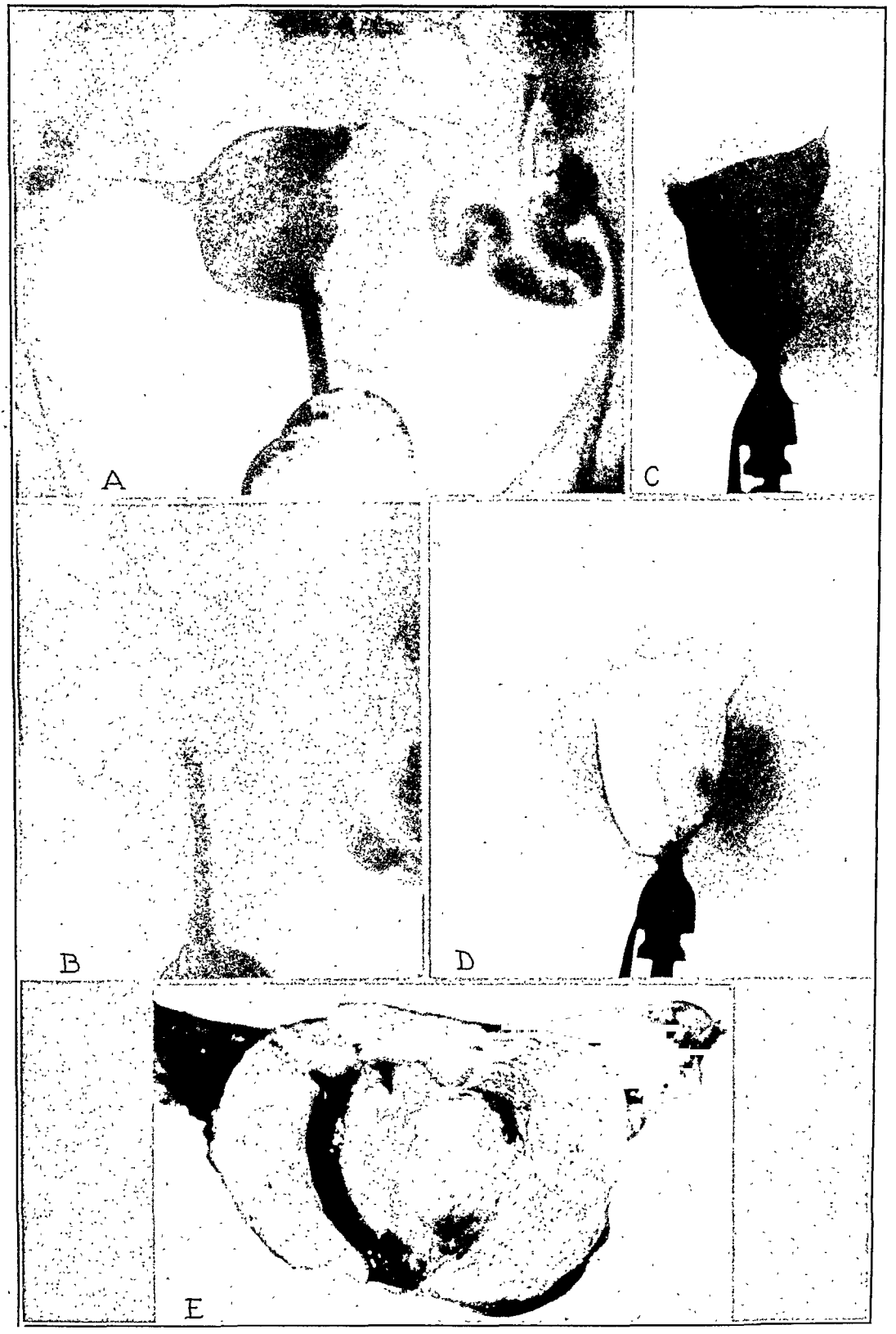
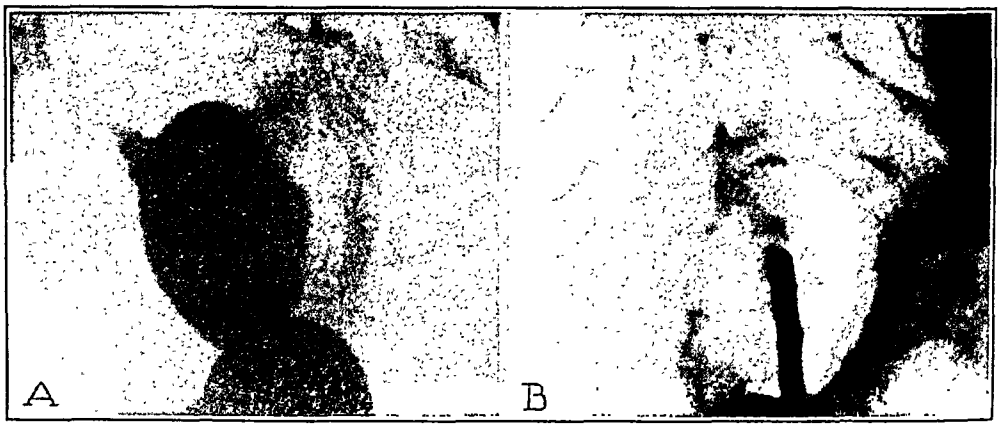
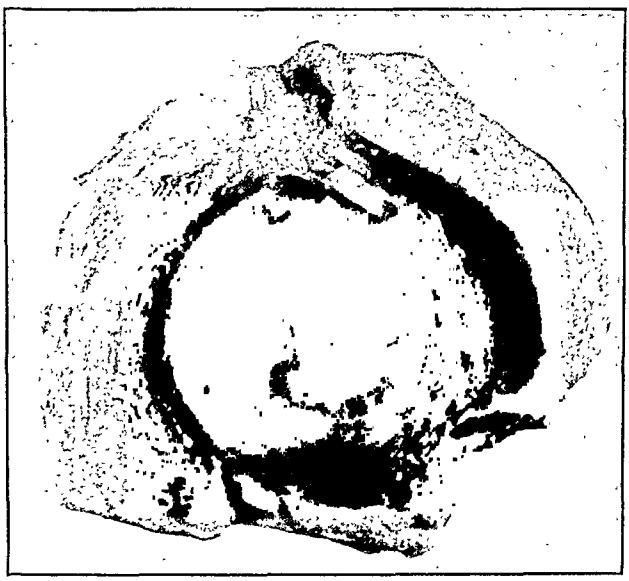


Fig. 3.—Case M. M. *A*, Clinical hyterogram with hippuran 100 per cent solution shows a dilated cavity without any definite indication of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran shows the uterine cavity to be definitely encroached upon by a submucous myoma. *C*, Hysterogram of extirpated uterus with hippuran 100 per cent solution; no indication of a submucous fibroid. *D*, Hysteroaerogram of extirpated uterus with CO_2 after hippuran shows the solitary submucous fibroid practically as it appears in Fig. 3, *E*. *E*, Uterus cut open shows the submucous fibroid visualized in hysteroaerogram, Fig. 3, *D*.





C.

Fig. 4.—Case I. G. *A*, Clinical hysterogram with hippuran 100 per cent solution shows an irregular shadow not particularly diagnostic of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran shows the submucous fibroid projecting into the uterine cavity as seen in the specimen (Fig. 4, *C*). *C*, Uterus cut open showing the solitary submucous fibroid.

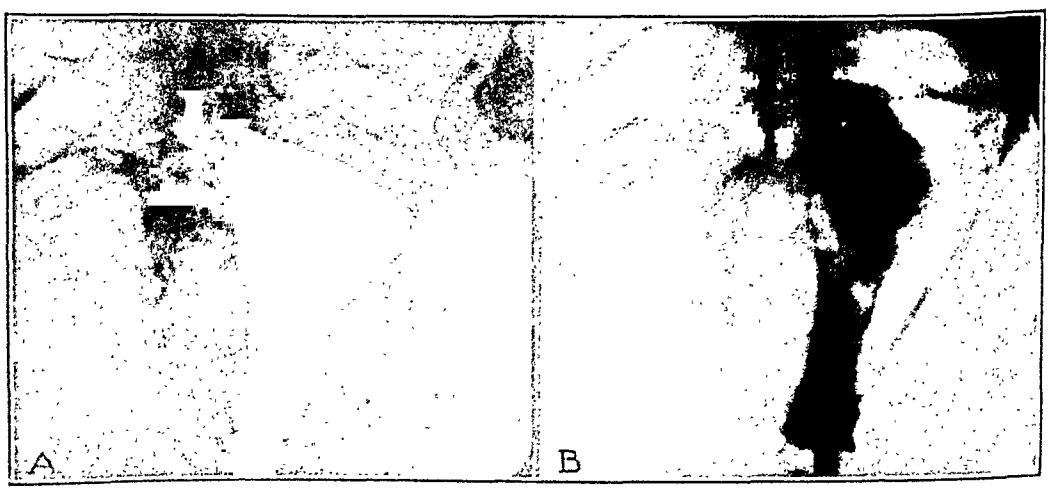


Fig. 5.—Case S. K. *A*, Clinical hysterogram with hippuran 100 per cent solution shows a dilated triangular uterine cavity; no suggestion of a submucous fibroid. *B*, Clinical hysteroaerogram with CO_2 injection after hippuran shows the submucous fibroid.

When no submucous myoma is present despite the multiplicity of the tumors, the uterine cavity may be typically triangular as in Fig. 8, *A* and *B*, Case M. E., where the cavity is only moderately dilated; or Fig. 9, *A* and *B*, Case T. B., where the cavity is very markedly dilated without any protrusion into it of any of the fibroids. The CO_2 x-ray contrast film, however, demonstrates this characteristically as may be seen in Figs. 9, *B* and 10, *B*. Solutions in the strengths employed for intravenous or retrograde urography are not quite strong enough to leave a deposit

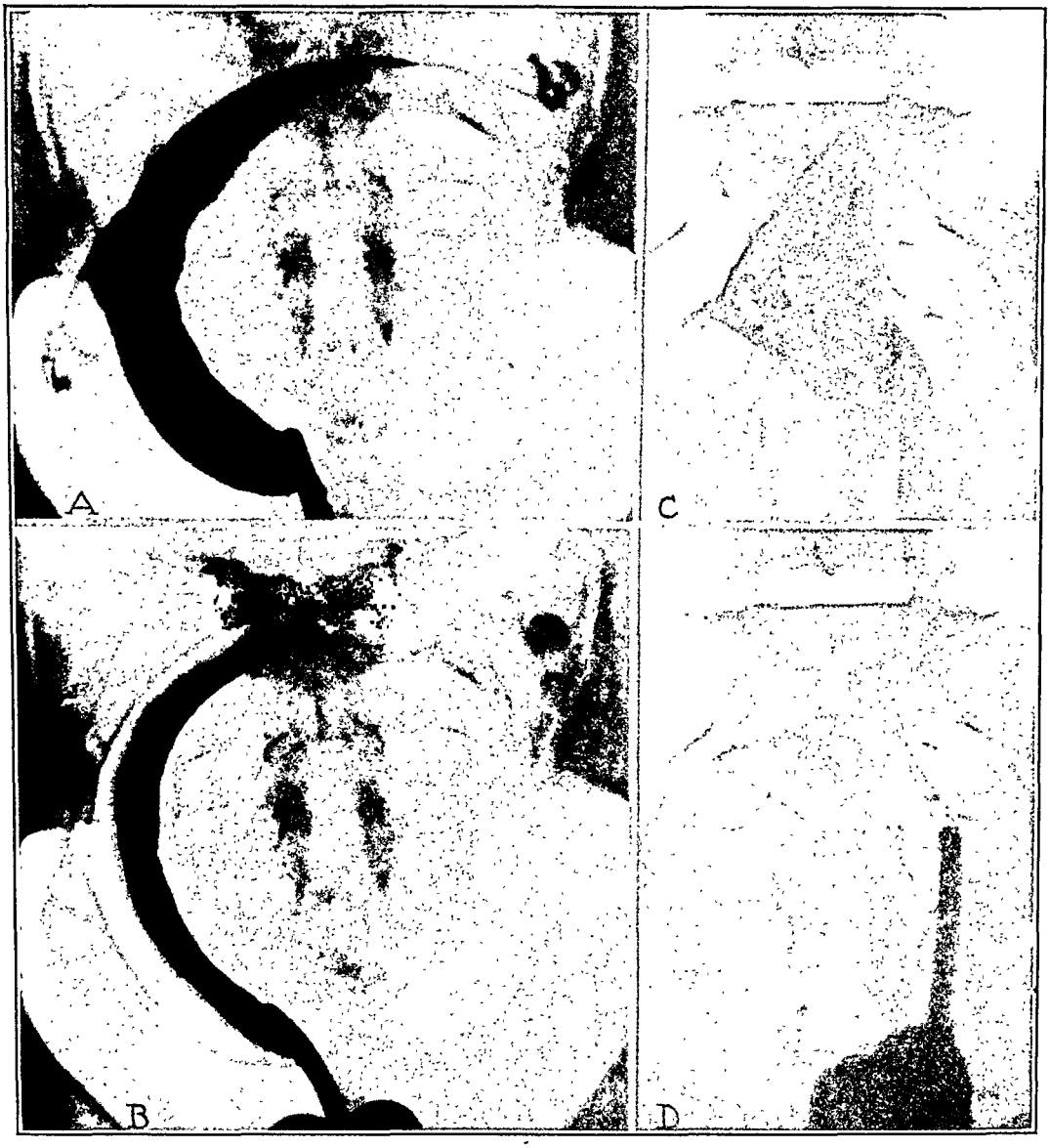


Fig. 6.—Case P. B. *A*, Clinical hysterogram with hippuran 100 per cent solution shows a dilated crescentic uterine cavity suggestive of submucous myoma. The tubes have been entered by the hippuran. *B*, Clinical hysteroaerogram with CO_2 injection after hippuran shows the submucous nature of the tumor. The tubes are still seen to be filled. *C*, *After myomectomy.* Clinical hysterogram using hippuran 100 per cent solution showing a triangular uterine cavity. *D*, *After myomectomy.* Clinical hysteroaerogram after CO_2 injection shows a triangular uterine cavity; no protrusion into it.

upon the uterine mucosa to serve as contrast with CO_2. We found that strengths of 80 per cent and upward gave better results. CO_2 is preferable to air because it avoids all possibility of embolism, being absorbed by an equal quantity of blood, while air and its other components, oxygen and nitrogen, are relatively insoluble.

The indications for the use of x-ray and radio-opaque media and CO_2 for the demonstration of submucous myoma may be briefly given:

1. When it is important to avoid a laparotomy for fibroids as in the case of obese individuals and in systemic disease, in which circumstances x-ray and radium therapy are usually preferred. If a submucous myoma is positively known to be present, surgical removal is indicated despite the increased risk to the otherwise handicapped patient.

2. When considering myomectomy in younger individuals who are sterile and desire children, or when menstruation is to be conserved,

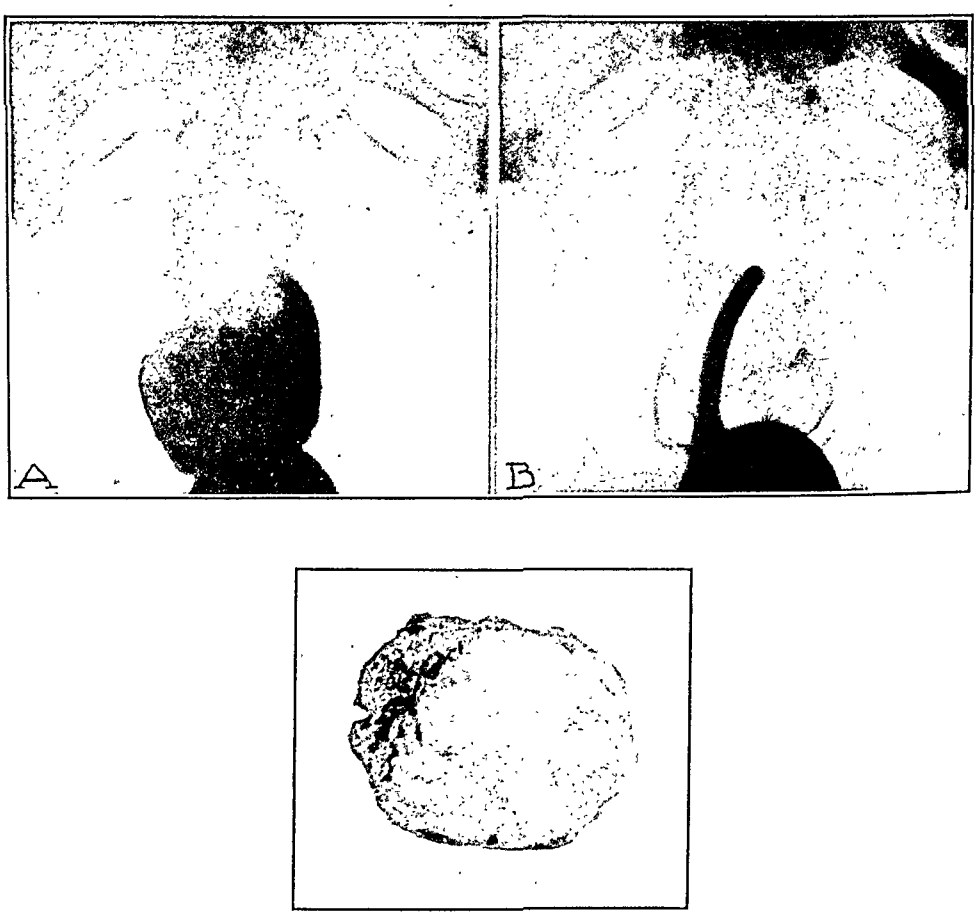


Fig. 7.—Case C. S. *A*, Clinical hysterogram with hippuran 100 per cent solution showing an irregular cavity without characteristic signs. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran showing the submucous character of the tumor. *C*, Extirpated uterus cut open showing the submucous myoma.

the knowledge of the presence of a submucous myoma will enable the surgeon to deal adequately with the condition, adopting suitable vaginal or laparotomy technique, or a combination of the two.

The cases in which hippuran and CO_2 were employed are the following:

Case E. C., 52 years old, gravida ii, para ii; menorrhagia for two years, flow increasing from three- to an eight-day flow with clots. Uterus enlarged to the size of a four months' gestation. Hysterectomy and bilateral salpingo-oophorectomy. Specimen injected with hippuran and CO_2 showed multiple submucous fibroids (Figs. 1, *A* and 1, *B*).

Case B. H., 42 years old, gravida ii, para ii; complained of menorrhagia of one year's duration and severe dysmenorrhea, periods lasting six to seven days instead of three to four. Uterus enlarged to size of a two and one-half months' gestation; cervix normal; adnexa not palpable. Hysterectomy. Specimen revealed by hippuran and CO_2 a single plum-sized submucous fibroid on a sessile pedicle (Fig. 2, *C*).

Case M. M., 47 years old, gravida iii, para iii; menorrhagia and dysmenorrhea for the past four to five months, periods increased from four to eight days, the flow being

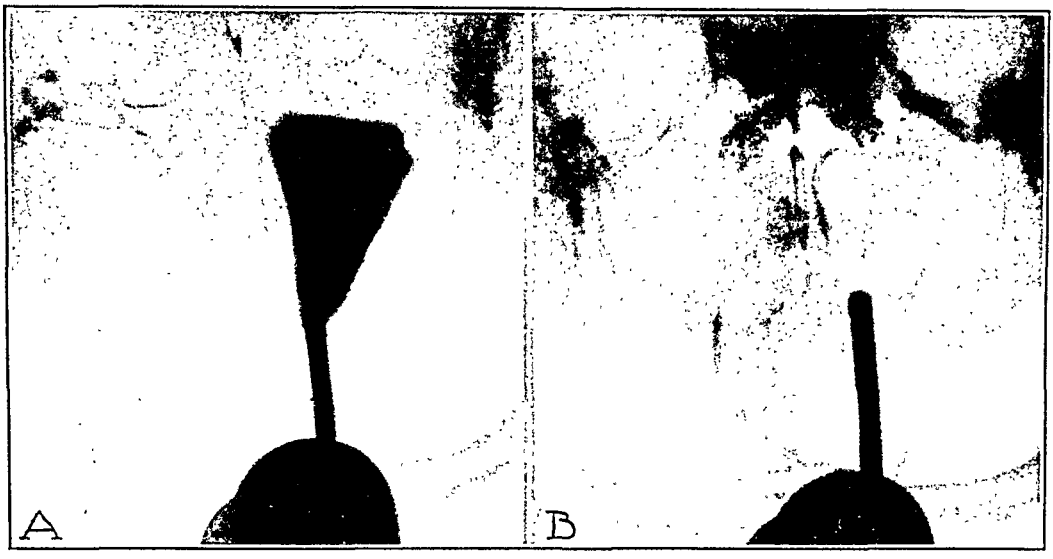


Fig. 8.—Case M. E. *A*, Clinical hysterogram with hippuran 100 per cent solution showing a somewhat dilated cavity with no suggestion of submucous myoma. *B*, Clinical hysteroaerogram after CO_2 injection shows a triangular cavity with no encroachment.

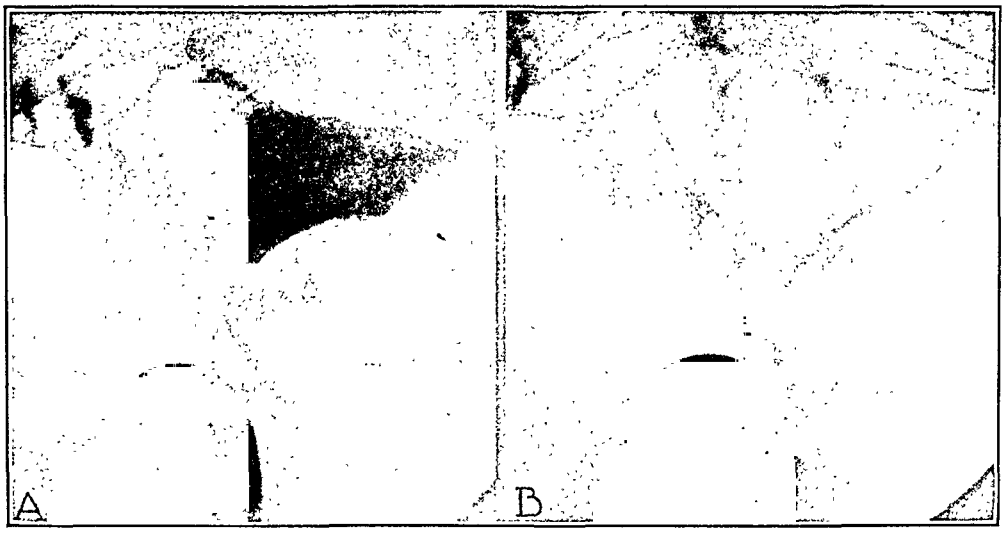


Fig. 9.—Case T. B. *A*, Clinical hysterogram with hippuran 100 per cent solution showing a widely dilated irregular uterine cavity. *B*, Clinical hysteroaerogram with CO_2 injected after hippuran showing no encroachment upon the uterine cavity.

profuse. Uterus enlarged to the size of a ten to eleven weeks' gestation; adnexa not palpable; cervix normal. Clinical hysterogram, hippuran and CO_2, showed a submucous myoma. Hysterectomy and bilateral salpingo-oophorectomy. Specimen showed a uterus enlarged to a three months' pregnancy, containing one large submucous fibroid and a few intramural fibroids (Fig. 3, *D*).

Case I. G., 43 years old, gravida ii, para ii; for past six months severe menstrual bleeding with passage of clots. Uterus uniformly enlarged to the size of a three

months' gestation. Clinical hysterogram, hippuran and CO_2, showed the presence of a large submucous myoma, Fig. 4, *B* (specimen), which was confirmed by the opened specimen.



Fig. 10.—Case F. W. *A*, Flat plate showing faint outline of enlarged uterus in relation to pelvis. *B*, Clinical hysterogram with hippuran 100 per cent solution showing a widely dilated irregular uterine cavity without any definite sign of submucous encroachment. *C*, Clinical hysteroaerogram with CO_2 injected after hippuran showing the submucous character of the fibroid. *D*, *After myomectomy.* Clinical hysterogram with hippuran 100 per cent solution showing widely dilated uterine cavity of triangular shape. *E*, *After myomectomy.* Clinical hysteroaerogram with CO_2 injected after hippuran showing a widely dilated uterine cavity; no submucous encroachment.

Case S. K., 48 years old, gravida v, para iv; craniotomy; and an angioma of the skull removed six months ago. Became pregnant, last period occurring on Dec. 20, 1937; an x-ray abortion was performed. Entered hospital bleeding profusely. Uterus the size of a three and one-half months' gestation and contained a number of subserous fibroids; cervix patulous; adnexa not palpable. Bleeding continued despite oxytocics, and a dilatation and curettage were performed. This revealed a submucous fibroid on the right posterolateral wall of the uterus, confirmed by a clinical hysterogram, hippuran and CO_2, Fig. 5, *B*.

Case P. B., 25 years old, single, gravida 0, para 0; menorrhagia for the past eight to nine months, flow increased from five to six to twelve to thirteen days. Uterus the size of a three months' gestation, smooth in contour, mobile; cervix firm, closed; adnexa negative. Clinical hysterogram (hippuran and CO_2) showed the presence of a submucous myoma (Fig. 6, *B*). Myomectomy was performed; one large fibroid removed from the left uterine wall. The postoperative injection of hippuran and CO_2 showed a return to the triangular form of the uterine cavity (Fig. 6, *D*).

Case C. S., 43 years old, married 9 years, gravida 0, para 0; menses normal until one year ago; since then has had menorrhagia and dysmenorrhea; flow eight to ten days with many clots. Uterus enlarged to size of a seven to eight weeks' gestation and slightly irregular; cervix softened and external os slightly dilated; adnexa negative. The lower pole of the intrauterine tumor was just palpable to finger tip. Clinical hysterogram not necessary but done for purposes of demonstration and contrast (Fig. 8, *B*). Vaginal hysterotomy and removal of a submucous fibroid the size of a large plum (Fig. 7, *C*).

Case M. E., 44 years old, gravida vi, para v; menorrhagia of one year's duration. Uterus enlarged to the size of an eight weeks' gestation due to a number of small myomas in the right uterine wall. Curettage: uterine cavity symmetrical showing no submucous tumors. Clinical hysterogram, hippuran and CO_2, showed moderately dilated triangular uterine cavity, no submucous myoma.

Case T. B., 49 years old, gravida ii, para ii; menorrhagia for past year. Blood pressure 200/100. Pelvic examination: cervix hypertrophied; uterus enlarged to the size of a two to two and one-half months' gestation; adnexa not palpable. Clinical hysterogram, hippuran and CO_2, showed the uterine cavity dilated but not encroached upon by any tumor (Figs. 10, *A* and *B*). Curettage and radium, 1,500 mc. hours.

Case F. W., 29 years old, single, nulligravida; profuse regular periods; increasing size of abdomen and metrorrhagia of three weeks' duration on two occasions. Uterus found enlarged to the size of five months' gestation, firm and tender. Clinical hysterogram, hippuran and CO_2, showed a markedly dilated, irregular uterine cavity on one side suggestive of a submucous myoma (Fig. 10, *B*) which was definitely proved after the injection of CO_2 (Fig. 10, *C*). A single large fibroid was removed without entering the endometrial cavity although the fibroid encroached upon the entire left side of the cavity. A hysterogram with hippuran and CO_2 after the operation showed the endometrial cavity of triangular configuration (Fig. 10, *D*) and after CO_2 injection (Fig. 10, *E*).

SUMMARY

The presence of submucous myomas can be diagnosticated roentgenologically by the intrauterine injection of hippuran followed by CO_2. Neither by itself is adequate for this purpose. The hippuran is used in concentrations of 80 to 100 per cent which, when expelled from the uterine cavity, leaves a crystalline deposit on the uterine mucosa and the mucosa covering the submucous tumor. The injection of CO_2 serves as a transparent contrast to the densely opaque hippuran outline. Both media are innocuous, each being well tolerated by the organism. There are no irritation and no residue or foreign body reaction. In selected cases where recognition of submucous myoma is important from the viewpoint of the choice of therapy, this method appears to be serviceable.

BREECH PRESENTATIONS AND PROPHYLACTIC EXTERNAL CEPHALIC VERSION

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MUCH has been written on the subject of breech presentation, its high fetal mortality and maternal morbidity, and the proper methods of delivering these patients. In many studies emphasis has been placed upon the management of the breech for the purpose of lowering the fetal mortality. Cannel and Dodek have shown in a review of the literature that, no matter what method is employed in delivering a breech presentation, the fetal mortality still remains too high. Further, it was shown that the greatest cause of fetal death is the result of injury rather than of asphyxia. It is our purpose to add to the literature the results of our study on breech presentations and to lay special emphasis upon the value of prophylactic external cephalic version as a prenatal method of treating breech presentations by which the fetal mortality may be materially reduced.

MATERIAL

We studied 167 primary breech presentations delivered at the University Hospital from 1926 to 1935. We eliminated all multiple pregnances where one or both babies were delivered as a breech, as well as all internal version and breech extractions.

In Table I are noted the distribution of the cases as to parity and types of presentations. It is interesting that the primigravida and multigravida are practically equal in number. This is somewhat unusual since breech presentations are usually considered more common in the multigravida.

In this same table we find that full breech and frank breech presentations, as well as the anterior types of breech presentations are in great preponderance.

In Table II are listed the various methods of delivery employed and the relationship of the fetal mortality to each type of delivery. Except for cesarean section deliveries we find that there is no marked difference in the fetal mortality and for each type the fetal mortality is high. In only two cases were the forceps applied to the aftercoming head.

It is interesting to know that in 39 cases of breech deliveries a single mediolateral episiotomy preceded the delivery; in 24 cases a bilateral episiotomy was used; and only in one case was a central episiotomy performed. Perineal lacerations were noted in 7 cases. This low incidence of lacerations is due to frequent use of episiotomy preceding most breech deliveries. In only one case was the Voorhees' bag employed to aid in the dilatation of the cervix, while in 8 cases manual dilatation of the cervix was necessary to effect delivery.

In attempting to find the etiologic factors responsible for the breech presentations exclusive of multiparity, we found that in 19 cases prematurity was present; in 2 cases monstrosity could be indicted; and in 58 cases contracted pelvis from a

TABLE I. SUMMARY OF BREECH DELIVERIES

Total number of primary breech deliveries	167
Primigravida	84
Multigravida	83
Full breech	52
Frank breech	79
Footling	14
Not classified	25
L. S. A.	72
R. S. A.	74
L. S. P.	10
R. S. P.	6
R. S. T.	1
Not noted	4

TABLE II. METHOD OF DELIVERY AND FETAL MORTALITY

TYPE OF DELIVERY	NO. OF CASES	MORTALITY
Breech extraction alone	71	27%
Break-up of breech and extraction	43	30%
Spontaneous delivery	38	41%
Cesarean section	12	0
Not noted	3	0

slight to a marked degree was noted. There were 12 cesarean operations done; in 8 cases for contracted pelvis; 2 for placenta previa; one for premature separation of the placenta; and one for the purpose of sterilization.

The duration of labor was found to be increased averaging 22.2 hours for the primigravida and 13.67 hours for the multigravida.

Very few accidents due to the breech presentation were encountered. Prolapse of the cord occurred in only 5 cases and in one case the arm was prolapsed as well. There were no clavicle nor femur fractures reported, and the only injury noted was a contusion of the thigh and arm in two cases.

TABLE III. CAUSES OF FETAL DEATH IN BREECH PRESENTATIONS

Intracranial hemorrhage	7
Asphyxia	21
Atelectasis	2
Monstrosity	2
Prematurity	7
Eclampsia	2
Maternal syphilis	4
Unknown	2
Total	47 (28.1%)

TABLE IV. FETAL DEATHS ASSOCIATED WITH OBSTETRIC ACCIDENTS

Total fetal mortality		47
Premature separation of the placenta	7	
Nephritic toxemia	1	
Eclampsia	2	
Hydramnios	1	
Syphilis	4	
Bandl's contraction ring	1	
Placenta previa centralis	1	
Pyelitis	1	
Monstrosity	2	
Prematurity	7	
	27	
Corrected fetal death	20 (12.1%)	

The gross fetal mortality in this series was 47 (28.1 per cent) with a corrected mortality of 20 (12.1 per cent). In Table III are listed the various causes of fetal death. In view of the fact that very few of these babies came to necropsy, it is most probable that the high number of fetal deaths ascribed to asphyxia was perhaps due to birth injury. In Table IV are listed the fetal deaths as they were associated with obstetric accidents.

There were three maternal deaths. One was due to multiple emboli following the delivery. Another was due to chronic myelogenous leucemia; and the third was due to shock and postpartum hemorrhage following premature separation of the placenta. It is felt that none of these deaths could be attributed to the type of presentation nor to the delivery.

The maternal morbidity was definitely increased; in 31 cases there was an elevation of temperature to 100.4° F. or more on two consecutive days. Most of these infections were mild. This gave us a morbidity of 18.56 per cent which is an expected finding in breech deliveries.

PROPHYLACTIC EXTERNAL CEPHALIC VERSION

From this study, which is essentially in agreement with all other studies on breech presentations and deliveries, we can readily understand the undesirability of the breech presentations and the inability to markedly improve our results by breech deliveries.

We must, therefore, look to some other method of handling the breech presentations that will make it possible to obtain more desirable results. External cephalic version seems to offer the one method by which this may be accomplished. If it is successful, we immediately convert a fetal mortality of approximately 15 per cent in breech presentations to one of 3 per cent in cephalic presentations.

King and Gladden; Irving and Goethals; and Cannel and Dodek recommend external cephalic version. Also the reports of Gibberd, Ryder, Bartholomew, McGuinness, Glassman, Végh, Thornhill and others who have performed external versions are convincing. Despite these favorable reports we still find either a resistance or an indifference among the profession to perform external version. Obstetric textbooks recommend that external versions should be attempted, yet we fail to teach this art to our students, and we hesitate to practice it upon our patients.

We have performed external version from the twenty-eighth to the thirty-eighth week of pregnancy; however, the best time is generally from the thirty-second to thirty-sixth week, although it should be attempted even at term or early in labor. The technic of external cephalic version we have employed is the same as described in any standard textbook on obstetrics. We believe it is important, however, to emphasize certain points in the procedure and to take certain precautions in performing a version. If the abdomen is well powdered, it will facilitate the movements of the hands over the abdomen. The version should be done slowly and gradually; if the uterus undergoes contraction, the baby is held in place but no further pressure is made until the uterus is relaxed. In this manner the turning is continued so that it may take ten or fifteen minutes before the version is completed. The fetal heart beat should be obtained before, during, and for several minutes after the version in order to ascertain its rate, regularity, and character. In this manner we make certain that there

is no marked change in the fetal heart due to the version. We have often noted a temporary change in the rate and regularity of the fetal heart following a version but never a persistent one. If the fetal heart after five minutes of auscultation should show a persistent slowing or increase or irregularity, it would probably be safer to undo the version. We do not advocate the use of an anesthetic, because it carries with it the risk of employing too great a force which may result in premature separation of the placenta. We feel that if a version cannot be performed without an anesthetic, it is better to leave it undone, because it is probably due to two causes; (1) the breech is already tightly fixed in the pelvis; or (2) a frank breech may be present. If a version cannot be done with a reasonable amount of pressure then an x-ray picture should be taken to ascertain the type of presentation. If a frank breech is present, a version should not be done: (1) the extended legs splint the body so that the baby cannot be made to flex sufficiently to make the version easy; (2) a compound presentation may result.

McCullogh reports 4 cases of external version in unrecognized frank breech presentation. These patients were permitted to go into labor and allowed to remain in labor for many hours without recognizing that the dystocia was due to a compound presentation; both feet and head presenting at the same time, with the final outcome being rupture of the uterus in all four cases. In our series we found two cases where the external version was unsuccessful; the x-ray picture showed frank breech presentations.

Since 1936 we have attempted to perform external cephalic version upon breech presentations which have come under our observation. These cases were gathered from the University Obstetrical Clinic, the Baltimore City Hospital and Baltimore City Health Department Pre-Natal Clinics, the Franklin Square Hospital and from the senior author's private case files. We have followed 77 cases of breech presentations; in 68 cases versions were attempted and in 55 versions were successful and delivered as cephalic presentations. In 2 cases versions were successful, but later the presentations reverted to breech and delivered as such. In 9 cases versions could not be performed. In 3 cases version was unsuccessful but spontaneous versions occurred later. In 6 cases no version was attempted and spontaneous version took place. In 3 cases of transverse presentation in which the breech was the original presentation version was successful.

TABLE V. TOTAL NUMBER OF BREECH PRESENTATIONS FOLLOWED (77)

No. of versions attempted	68	
No. of successes	55	(81%)
No. of primigravida	21	
No. of successes in primigravida	15	(71.4%)
No. of multigravida	47	
No. of successes in multigravida	40	(85.3%)
Resulting Presentations:		
Occiput anterior	43	(78.2%)
Occiput posterior	7	
Rotation from occiput posterior or occiput transverse to occiput anterior	5	
Gross fetal mortality	1	(1.82%)

In Table V we give a summary of our results on external versions. It is important to point out the 71.4 and 85.3 per cent successes in primigravida and multigravida, respectively, as well as the 78.2 per cent resulting anterior occiput presentations,

In 14 cases the pelvis was contracted. A total of 22 forceps deliveries were performed; 13 of these were forceps deliveries done for convenience and 9 for indicated reasons. There were 4 cesarean operations; 3 in vertex presentations for disproportion and one in a breech presentation where version failed and a contracted pelvis was present.

TABLE VI. COLLECTED CASES OF EXTERNAL VERSION

AUTHOR	CASES ATTEMPTED	CASES SUCCESSFUL	NO. WITH ANESTHESIA	PRIMIPARAS	MULTIPARAS	FETAL MORTALITY	PROLAPSE CORD	BLEEDING PREMATURE SEPARATION OF PLACENTA	COMPOUND PRESENTATION	REMARKS
Vedder	52	46	22			1 (2.18%)	0			
Thornhill	58	49	2	17	32	1 (2%)	0			2 sections
Mehta	55	53	0	8	47	0	0			
Davison	14	12	0			0	0			
Donovan	91	80	-	38	42	4 (5%)	0			
McGuinness	59	57	2	23	34	1 (1.8%)	0			
Glassman	64	61	0	9	52	0	0			
Ryder	29	20	6			0	0	1 (slight)		
Gibberd	232	179	5			7 (3.9%)	0	1 (slight)		
Rietdijk	356	317				12 (4.5%)	2			
Meurer	149	138								Quoted by Bartholomew
Kouwer	190	174	0			7 (4%)				
Meyer	22	21	0	3	18	1 (4.5%)			1	
Decugniere	32	29	0	12	17	0				1 Cesarean delivery
Sarocy	23	20								Quoted by Horn
Pollack	16	16	7							
Bartholomew	54	39		53%	80%	0	0	0	0	
Aranowitch	66	36								Quoted by Horn
Végh	36	32	0	16	20	0		0		
Kende	7	6				0				
King, W. W.		250	38			4%				
White		300	92			5%		6		All 6 cases of bleeding under anesthetic
Allen		100		35	65	0				
Macaffee		134				0.74%				
Wrigley	76	45	76			10 (13.6%)	1	3		All cases done under an anesthetic
Siegel and McNally	68	55	1	15	40	1 (1.82%)	1	0	0	4 sections
Total		2269				3.13%				

Accidents due to the versions were practically none. There was no bleeding. There were only 2 cases of premature rupture of the membranes; 1 occurred twenty-four hours after and the other several days after the version. There were no premature labors. There was one case of prolapse of the cord and hand. This was in a multipara where version was performed early in labor and was successful. The labor progressed normally; the cervix became fully dilated and while the patient was being prepared for delivery her membranes ruptured with such great force that the amniotic fluid struck a wall about eight feet away. With this accident the cord and hand prolapsed together; the patient was immediately delivered of a live baby.

There were no maternal deaths and a maternal morbidity of 13 per cent resulted; all infections being mild.

There was one fetal death in the entire series of successful versions. This baby was delivered spontaneously at home before the arrival of the doctor, who found the baby lying in a pool of amniotic fluid with a loop of cord about its neck. This baby evidently died of external asphyxia from drowning.

In our series of 58 patients only one version was necessary; in 5 patients, 2 versions; in 2 patients, 3 versions; and in 1 patient, 4 versions were done. There apparently is no danger in performing repeated versions. At no time did we employ abdominal binders nor do we believe them to be of value.

Bartholomew reports that by performing external versions he had reduced the incidence of breech deliveries by 80 per cent. The incidence of breech presentations at the University Hospital for ten years prior to 1936 was 5.43 per cent. For the years 1936 and 1937, by performing a limited number of external versions since not all breech presentations came under our care, this incidence was reduced to 3.78 per cent.

DISCUSSION

The objections to performing external cephalic version are generally given as premature rupture of the membranes; premature labor; premature separation of the placenta; prolapse of the cord; twisting of the cord about the baby's neck or body; reversion back to breech; compound presentation; rupture of the uterus; intrauterine death and finally that spontaneous version does occur. These are all valid objections but to determine their frequency and their effect upon the fetal mortality, we have gathered together in Table VI the reports of many writers on this subject. From this we find that the gross fetal mortality except for Wrigley's series varied from 5 per cent to nothing. In Wrigley's series we find that all the versions were done under anesthesia with a high incidence of bleeding and resultant high fetal mortality. Wrigley warns against the use of anesthesia, because of the too great force employed in executing the version. Otherwise the complications following versions were very few. Thus in a total of 2,269 successful versions, there resulted a gross fetal mortality of 3.13 per cent, which is what one expects even in cephalic presentations.

We recommend doing a cephalic version in the face of existing contracted pelvis as a valuable procedure. It is impossible to adequately judge disproportion clinically in the case of a breech presentation; and roentgen cephalometry is very unsatisfactory in these cases. Goethals has shown that the technic is complicated and that in 39 per cent of the films taken, measurements could not accurately be made. In cephalic presentations the x-ray measurements are more

satisfactory and clinically one can determine whether disproportion exists and whether a test of labor should be given. We wish to report four cases which graphically illustrate the value of cephalic version in contracted pelves:

CASE 1.—A 16-year-old negress, primigravida with a rachitic pelvis whose C.D. measured 9.0 cm. and x-ray C. V. 8.4 cm. was seen on July 13, 1937 with a presentation of L. S. T. and converted by external version to L. O. A. A test of labor was given, the head entered the pelvis and after a labor of 12¼ hours delivered spontaneously of a live baby weighing 6 pounds and 1 ounce. With these measurements and failure to have performed a version, we would have delivered her by an elective cesarean operation.

CASE 2.—A 19-year-old white woman, para i who, in her first pregnancy, had a breech presentation with the breech fixed in the pelvis. Attempts were made to perform an external version with and without an anesthetic but failed. X-ray cephalopelvimetry showed a borderline disproportion with a frank breech. She was delivered by an elective section of a live baby weighing 6 pounds 7 ounces. In her next pregnancy on Sept. 17, 1936 she was thirty-four weeks with an L. S. A. An external version was done changing the presentation to R. O. A. At term a test of labor was permitted, the head entered the pelvis and after a labor of twelve hours and ten minutes, she was delivered by low forceps after a manual rotation from R. O. T. to R. O. A. of a live baby weighing 6.5 pounds. Had we failed to have done the version in this case she would have been delivered by a second cesarean section.

CASE 3.—A 21-year-old negress, gravida iii, who had a generally contracted pelvis, was delivered in her first pregnancy of a stillborn baby by cesarean section. The reason for the section was not known. In her second pregnancy she had a breech presentation with no attempt at conversion. It resulted in a footling presentation and during the extraction both arms became extended in the nuchal position, the clavicle was accidentally fractured and finally a live baby weighing 6 pounds 2½ ounces was delivered. With her third pregnancy on Oct. 6, 1936 an L. S. P. was converted by external version to R. O. T. She was delivered on Dec. 2, 1936 after a labor of eight hours and fifty-four minutes by low forceps after manual rotation from R. O. P. to R. O. A. of a live baby weighing 6 pounds 4½ ounces. Thus in this case we obviated the difficulties of a breech delivery.

CASE 4.—A 21-year-old negress, primigravida, with a contracted pelvis had on Sept. 29, 1937 an L. S. A. at thirty-eight weeks converted by external version to R. O. T. On Oct. 13, 1937 she went into labor with suggestive disproportion and was given a test of labor. The head failed to enter the pelvis and she was delivered by a low cervical section of a live baby. If this case had been permitted to have remained a breech, a test of labor would have been of no real value, because the soft breech would enter the pelvis, whereas, the aftercoming head would not; and it would have been too late then to perform a cesarean section.

There have been reported sporadic cases of fetal death in utero following external version. That has not been our experience nor that of most writers. It is quite possible that these deaths may have been coincidental, since a certain number of babies die in utero without any discernible cause.

SUMMARY

1. A study of 167 primary breech deliveries is presented.

2. The etiologic factors responsible for breech presentations aside from multiparity seem to be prematurity, monstrosity, and contracted pelves.

3. This study reveals a gross fetal mortality of 28.1 per cent and a corrected one of 12.1 per cent.

4. It is believed that the fetal mortality in breech deliveries cannot be reduced below a certain minimum, which is still too high, due to inherent anatomic difficulties present.

5. External cephalic version offers a satisfactory method by which the high fetal mortality in breech deliveries can be reduced.

6. In this series external version was successful in 81 per cent of the cases with the resultant presentation being occiput anterior in 78.2 per cent.

7. External version should be performed without anesthesia, slowly with auscultation of the fetal heart before, during, and after the version.

8. If version cannot be performed with a reasonable amount of force, an x-ray picture should be taken to rule out a frank breech, which should not be turned.

9. Carefully done external versions result in few accidents and in good outcome for the baby.

10. An external version in the face of a contracted pelvis is desirable in order that better clinical judgment may be used in the treatment of the case.

11. The practice of external cephalic version as a prophylactic measure in prenatal care should be taught and employed in order to reduce the incidence of breech deliveries with its high fetal mortality.

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During 1914 to 1933 there were 47,793 deliveries at the Helsingfors Woman's Clinic. During the first ten-year period there were 22,196 deliveries with a maternal death rate of 0.45 per cent. During the remaining years there were 25,597 deliveries with a mortality of 0.30 per cent. The most important causes of death were infection (61.8 and 45.9, respectively) toxemia (23.7 and 27.1 per cent), hemorrhage (9 and 8 per cent), and heart trouble (5 and 12 per cent). About 50 per cent of the patients who died were infected or moribund at the time of admission to the hospital. If these are excluded, the total maternal mortality for the two periods was 0.18 and 0.17 per cent, respectively.

J. P. Greenhill.

THE EFFECT OF QUININE-CALCIUM ON UTERINE MOTILITY

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ALTHOUGH quinine has long been recognized as an ecbolic drug, the results obtained with its therapeutic use have been variable and unpredictable.

Schübel[1] working on puerperal cats found that small doses of quinine amplified the uterine contractions while large doses depressed them, and he emphasizes therefore the importance of using small doses in obstetric practice. Weissmann and Klippel[2] on the other hand have not seen any depressing effect with larger doses of quinine, and they attribute the variable effects to differences in uterine sensitivity. In studying the effects obtained with combinations of quinine and various other oxytocic agents, Kunisho[3] found no potentiation of pituitrin effects with quinine on strips of human uterus, whereas in the case of excised rabbit uteri, pregnant or nonpregnant, he[4] found a combination of one-half the minimal active dose of each drug to be an effective stimulus.

More recent investigations have indicated that quinine is much more effective in increasing uterine motility when it is combined with calcium.

Winkler and Vetter[5] and Weissmann and Klippel[2] in clinical studies have reported very good results with quinine-calcium (Sandoz). They found that it greatly surpassed quinine alone not only in increasing the sensitivity of the uterus to pituitary extract but also for inducing labor pains. The main indication according to their investigations is primary uterine inertia particularly after premature rupture of the fetal membranes.

Weissmann and Klippel extended their work into the experimental field and tested quinine and calcium separately and in combination on multiparas and nonpregnant mice. The animals were killed shortly after application of the respective drugs, and kymographic registrations were made of the contractions of the surviving uteri. The contractions after quinine alone showed an increase in both frequency and amplitude, while with calcium alone only the amplitude was increased. When quinine and calcium were administered simultaneously the records showed a combination of the quinine and calcium curves.

Other investigations[6, 7] have indicated the usefulness of quinine-calcium in therapeutic abortions, and Busch[8] has employed it in the treatment of a variety of obstetric cases.

In the present investigation the uterine fistula for recording uterine motility in unanesthetized rabbits[9, 10] was used. Fully mature female rabbits, weighing from 2 to 3 kilograms, were ovariectomized and motility was induced and maintained by daily administration of the ovarian hormone, estradiol.

The preparations used were a solution of quinine dihydrochloride, the neocalglucon (calcium gluconogalactogluconate) ampoule product equivalent in calcium ion content to a 10 per cent supersaturated solution of calcium gluconate, and the regular quinine-calcium (Sandoz).[1] Each cubic centimeter of the quinine-calcium (Sandoz) ampoule product is said to contain 0.06 gm. of quinine gluconate

(equivalent to 0.037 gm. of anhydrous quinine base) and 0.009 gm. of calcium ion. These quantities of quinine (calculated as the anhydrous base) and calcium ion were contained respectively in each cubic centimeter of the quinine dihydrochloride solution and the neo-calglucon ampoule solution. Injections were made both intravenously and intramuscularly, in the former case the usual dose being 1.0 c.c. and in the latter 2.0 c.c. The rate of intravenous injections never exceeded 1.0 c.c. *per minute.*

The plan of procedure which was adopted for the most part was to run comparable experiments, so far as conditions permitted, using the various preparations on consecutive days on the same animal. This was deemed advisable for two reasons: (1) The effect from the quinine injections, even after intravenous administration, was found to last for as long as 1.5 to 2 hours; (2) in control experiments where no injections were made, uterine motility sometimes decreased appreciably within two

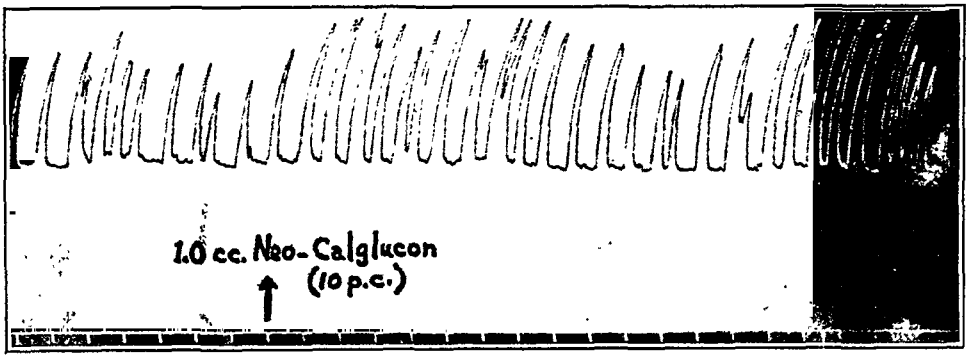


Fig. 1.—Effect of neo-calglucon (1.0 c.c. intravenously) on uterine motility. Time in minutes.

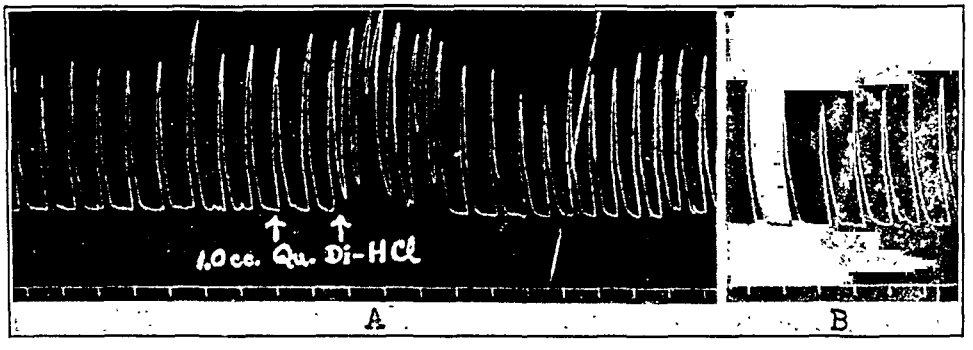


Fig. 2.—Effect of quinine dihydrochloride (1.0 c.c. intravenously) on uterine motility. (*A*) Immediately after, (*B*) one hour after injection. Time in minutes.

to three hours so that repeated injections might give unreliable and imcomparable results.

The procedure was varied somewhat in different experiments but the general rule was to allow fifteen to thirty minutes of normal recording and then make the injection without interrupting the record. In order to evaluate the records the height of each separate contraction was measured, and for comparing any given period with the normal the total contraction height for this period was divided by the number of minutes. Since it was necessary to establish a new normal for each separate experiment, the only way of comparing the effects of different injections was to express the results as percentage variation from the normal.

EXPERIMENTAL RESULTS

The records in general show that while quinine and calcium both produce an increase in uterine motility the effect produced by a combina-

tion of the two is appreciably greater and more prolonged than that with either alone. This is true for both intravenous and intramuscular injections.

Figs. 1 to 3 are typical records showing the effects of intravenous injections. In all three the increased motility is due primarily to an increase in the height of contractions, the rate showing no appreciable change except during the first few minutes after the injection when it is usually accelerated. In the case of both quinine preparations (Figs. 2 and 3) there is always a tendency for a sustained contraction for the first two or three minutes which becomes more pronounced if the injection is made with greater rapidity (see Fig. 4). This effect was not produced with calcium. The more prolonged effect of quinine-calcium as compared with that of quinine alone is shown by the records in part *B* of Figs. 2 and 3 which were made

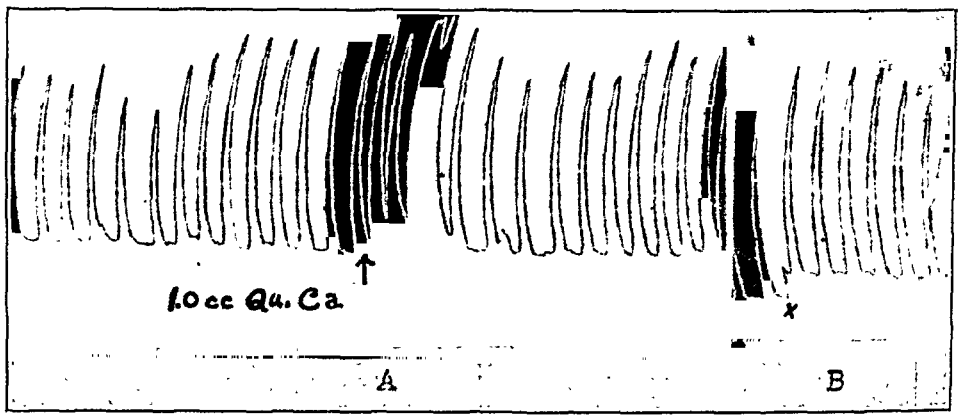


Fig. 3.—Effect of quinine-calcium (1.0 c.c. intravenously) on uterine motility. (*A*) Immediately after, (*B*) one hour after injection. Time in minutes. Base line readjusted at *X*.

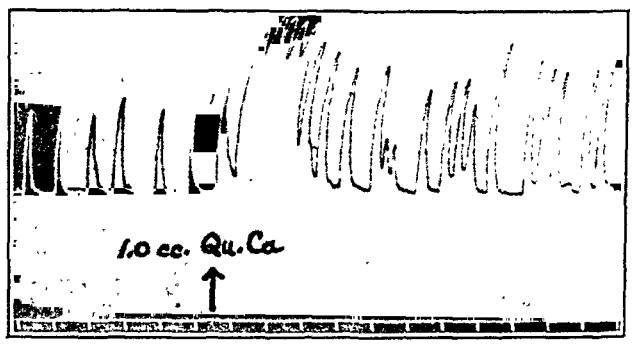


Fig. 4.—Effect of a more rapid injection of quinine-calcium (1.0 c.c. intravenously) on uterine motility. Time in minutes.

one hour after the injections. While the uterine motility in the quinine record has returned to normal, it is still markedly increased in the experiment where quinine-calcium was used.

A careful measurement of the records from a number of experiments shows that during the first thirty minutes after intravenous injections of 1.0 c.c. each of the three preparations used, the greatest increase in motility is given by quinine-calcium. The average figures obtained by such an analysis, expressing the increase in per cent, were: for quinine-calcium 33, for quinine alone 18.7, and for calcium alone 26.5.

When the injections are made intramuscularly the results are essentially the same except that the effects appear more gradually and continue longer. The tendency for sustained contractions with quinine is less evident and is often absent altogether. In Figs. 5, 6, and 7 are records showing the effects at periods up to two hours after intramuscular injections of neo-calglucon, quinine dihydrochloride and quinine-cal-

cium, respectively. There is a marked increase in uterine motility with each of the three preparations, but with a combination of quinine and calcium the effect is greater than with either alone. This difference becomes more pronounced in parts *B* and *C* which were recorded at forty-five and eighty-five minutes after the injections

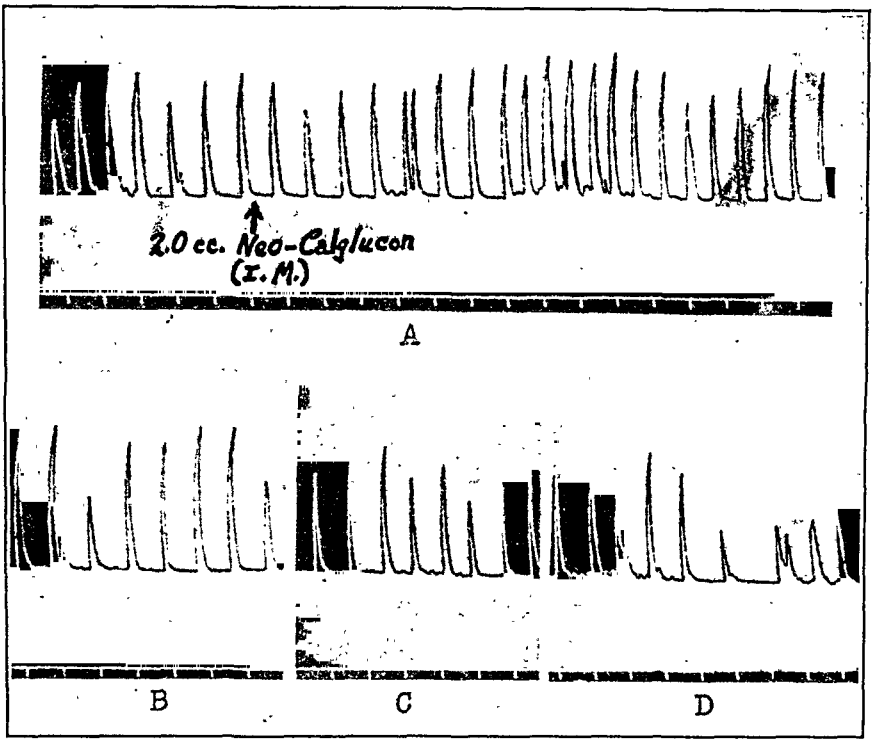


Fig. 5.—Effect of neo-calglucon (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

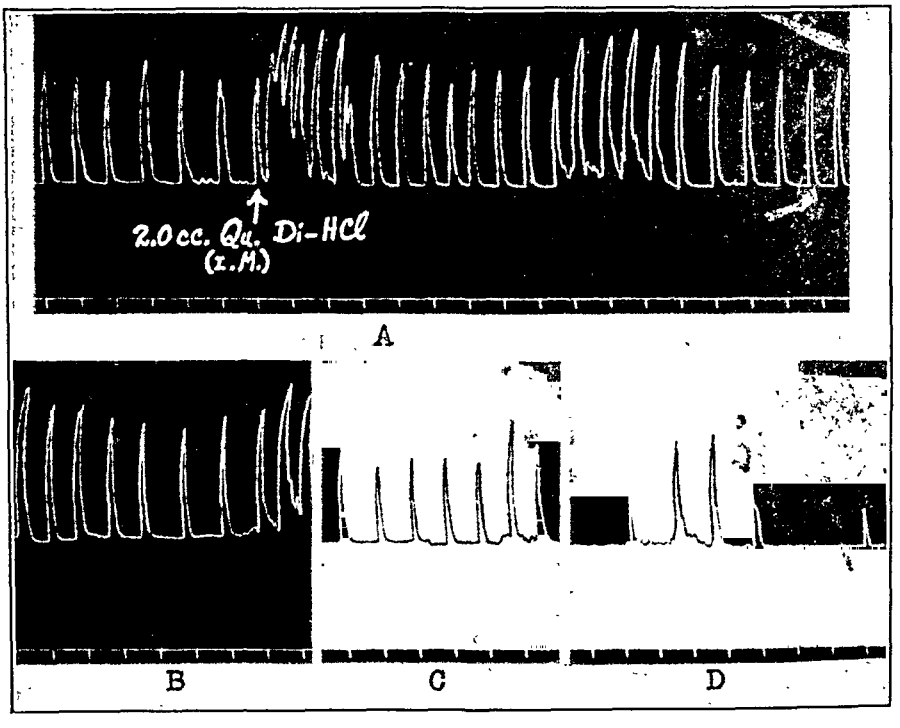


Fig. 6.—Effect of quinine dihydrochloride (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

were made. In part *D* (two hours after injection) of the records where calcium and quinine were used alone, the motility is decreased noticeably below the normal. The significance of this decrease seems doubtful in view of the fact that motility may begin to decrease after two hours of continuous recording in control experiments where no injections have been made. It is significant, however, that the motility two hours and even longer (see Table I) after quinine-calcium is approximately normal, whereas it may be depressed as much as 50 per cent the same length of time after an equivalent dose of quinine alone.

Table I which has already been referred to summarizes the data taken from the entire experiments shown in Figs. 5 to 7. These three experiments were run on the same animal on three consecutive days under practically identical conditions. After ninety minutes of continuous recording following the injections the record was stopped for thirty minutes. Changes in motility were computed over ten-minute intervals throughout, and with very few exceptions the values for quinine and calcium combined are seen to be definitely larger than for either quinine or calcium alone.

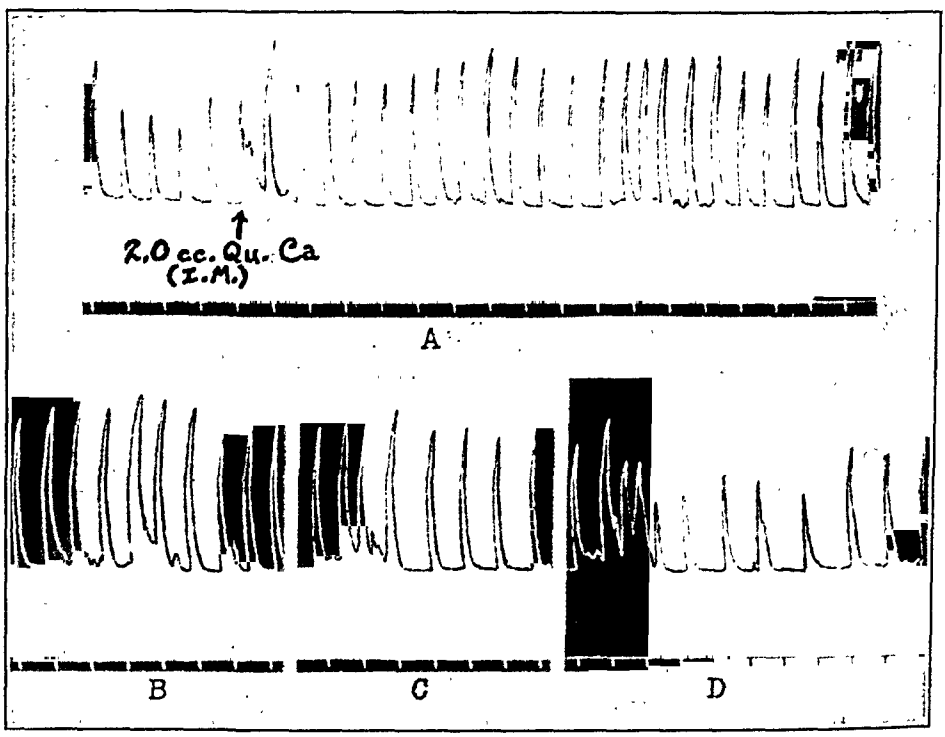


Fig. 7.—Effect of quinine-calcium (2.0 c.c. intramuscularly) on uterine motility. (*A*) Immediately after, (*B*) forty-five minutes after, (*C*) eighty-five minutes after, and (*D*) two hours after injection. Time in minutes.

As in the case of intravenous administration the calcium alone gives somewhat greater increases than the quinine alone. This of course may be purely a matter of dosage.

DISCUSSION

While the scope of this investigation is rather limited, particularly regarding the matter of dosage, the results are quite clear-cut. In the unanesthetized, nonpregnant rabbit with good uterine motility, quinine (in the dosage used) produces a greater effect when combined with calcium than when it is administered alone.

That calcium may have a stimulating effect upon uterine motility has been demonstrated both clinically and experimentally. Pieri[11] found that the weakened uterine contractions in a case of eclampsia were strengthened markedly after the injection of calcium. Reynolds[12] re-

TABLE I. CHANGES IN UTERINE MOTILITY FOLLOWING INTRAMUSCULAR INJECTIONS OF 2.0 C.C. EACH OF NEO-CALGLUCON, QUININE DIHYDROCHLORIDE AND QUININE-CALCIUM (SANDOZ). CHANGES ARE EXPRESSED AS PER CENT DEVIATION FROM THE NORMAL FOR TEN-MINUTE INTERVALS UP TO THREE HOURS

TIME AFTER INJECTION IN MINUTES	NEO-CALGLUCON (CALCIUM GLUCONOGALACTO-GLUCONATE)	QUININE DIHYDROCHLORIDE	QUININE-CALCIUM (SANDOZ)
0-10	+63	+91	+66
10-20	+64	+46	+97
20-30	+90	+56	+94
30-40	+79	+15	+79
40-50	+20	+44	+70
50-60	+47	+18	+60
60-70	+48	+33	+59
70-80	+39	+40	+30
80-90	+25	+29	+44
Record Stopped for 30 Minutes			
120-130	-22	-62	+ 5
130-140		-42	- 6
140-150		-51	- 7
150-160		-75	+ 8
160-170		-40	-21
170-180			+13

cording from uterine fistulas in unanesthetized rabbits obtained sustained contractions with intravenous and subcutaneous injections of calcium. That the effect is due to the calcium ions is supported by the fact that identical results are produced by calcium chloride and calcium gluconate and furthermore by the fact that the contractions can be inhibited by magnesium salts. In the present work the effect of the calcium has been primarily one of increased amplitude of contractions, with no indication of sustained contractions. Since the two investigations were carried out under almost identical conditions except for the time of year, the question arises as to whether the sensitivity of the rabbit's uterus may not undergo a seasonal variation.

The manner in which calcium potentiates the quinine effect on the uterus is not clear. The tracings obtained by Weissmann and Klippel[2] from the surviving mouse uterus after giving quinine and calcium together show a combination of two quite distinct effects which are produced by the quinine and calcium separately, viz., increased rate of contractions and increased amplitude of contractions. In the rabbit uterus, however, neither drug acting separately nor the combination of the two affects the rate appreciably, the amplitude only being increased. While the increase in motility after quinine-calcium is not equal quantitatively to the combined increases after equivalent amounts of quinine and calcium separately, the potentiation of effect may be simply of an additive nature. On the other hand this does not seem to explain adequately the more prolonged effect of quinine-calcium as compared with that of quinine or calcium alone.

Judging from the results that have been obtained with quinine therapy, there can be little doubt that the sensitivity of the uterus to quinine must vary greatly under different natural and experimental conditions. And while calcium alone may have the ability to augment

reached the period of viability and which cannot be expected to survive. The only justification for the use of "corrected mortality" figures is in those instances where an evaluation of a certain procedure makes it necessary to eliminate those cases in which the factor being investigated could not have played a contributing part. Citing "corrected mortality rates" as a hospital's actual mortality is never justified.

In the Chicago Lying-in Hospital from May 25, 1931, to Jan. 1, 1938, there were 17,728 deliveries, with 371 neonatal deaths and 402 stillbirths. The incidence of the various methods of delivery and the number of deaths occurring in each type are shown in Tables II and III.

TABLE II. INCIDENCE OF VARIOUS TYPES OF DELIVERY

	TOTAL NUMBER OF DELIVERIES	INCIDENCE PER CENT
Cephalic, natural	10,877	61.9
Cephalic, low forceps	3,995	22.5
Cephalic, midforceps	835	4.7
Breech	708	4.0
Cesarean section	1,041	5.8
Version and extraction	162	0.9
Miscellaneous	110	0.6

TABLE III. TYPE OF DELIVERY IN RELATION TO FETAL AND NEONATAL DEATHS

	TOTAL DELIVERIES	STILL-BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	PER CENT
Cephalic, natural	10,877	170	174	344	3.0
Cephalic, low forceps	3,995	22	35	57	1.4
Cephalic, midforceps	835	22	20	42	5.0
Breech	708	61	56	117	16.5
Cesarean section	1,041	31	62	93	8.9
Version and extraction	162	35	23	58	34.5
Miscellaneous (Includes 59 craniotomies)	110	61	1	62	56.3

It is important to know the incidence of the various fetal age groups and the mortality rates of the different groups. Table IV shows that our total rate per thousand live born infants is 44, with a stillbirth rate of 23 and a neonatal death rate of 21. If one considers only the previable infants and fetuses, the corresponding rates are 988, 462, and 526, respectively. The corresponding rates for the viable prematures are 346, 165, and 181, respectively, and for term infants, they are 18, 10,

TABLE IV. MORTALITY RATES IN RELATION TO FETAL AGE AT TIME OF DELIVERY

	TOTAL BIRTHS	TOTAL NEONATAL MORTALITY	NEONATAL MORTALITY PER 1,000 BIRTHS	TOTAL STILL-BIRTHS	STILL-BIRTH MORTALITY PER 1,000 BIRTHS	TOTAL MORTALITY PER 1,000 BIRTHS
Term	16,529	133	8	189	10	18
Premature	1,043	189	181	170	165	346
Previable	93	49	526	43	462	988
Undetermined	63	---	---	---	---	---
Total	17,728	371	20	402	22	43

and 8. These comparisons are striking and indicate the importance of the problem of prematurity.

Investigation of the incidence of births of the different groups shows that the number of prematures is relatively small, as in over 93 per cent of the births the infants were at term, in 5.8 per cent they were viable prematures, and in only 0.5 per cent were they previable (Table V).

TABLE V. TOTAL DELIVERIES FROM MAY 25, 1931 TO JAN. 1, 1938

	TOTAL NUMBER OF DELIVERIES	PER CENT
Term	16,529	93.30
Premature	1,043	5.80
Previable	93	0.50
Unrecorded	63	0.38
Total	17,728	

With a stillbirth rate of 36 and a neonatal rate of 34 for the United States, it is obvious that it is possible to secure an improvement in the fetal and neonatal mortality rates. This can be accomplished only by adequate maternal care. Inasmuch as fetal and neonatal deaths are largely due to conditions associated with childbirth, the problem is primarily an obstetric one. It is apparent that proper preconceptional and prenatal care would entirely eliminate fetal and neonatal disease due to syphilis. On the other hand it is quite obvious that with our present state of knowledge nothing can prevent disease and death due to malformations. Prematurity constitutes an extremely important problem. The only salvation for the previable group of premature infants is a prolongation of gestation. Whether or not gestation can be prolonged in these cases is a matter which must be determined in each individual case. Many previable births cannot be avoided but in some instances they can be, and in others the period of gestation can be prolonged to viability.

The methods of decreasing the number of deaths of premature infants are in the main two; first, the prolongation of gestation when it is feasible and safe; second, the provision of proper environmental conditions for the premature infant from the moment of birth. It must be recognized that in certain conditions such as the toxemias of pregnancy and nephritis, the prolongation of gestation is a hazard not only to the mother but also to the fetus and antenatal death may occur.

It is impossible to undertake to discuss in detail the procedures to be followed in treating the numerous complications of pregnancy and labor which would provide the greatest safety for the fetus as well as for the mother. Such analyses must be made, however, in relation to the causes of fetal and neonatal deaths and from them conclusions must be drawn as to which methods of treatment afford not only the maximum safety to the mother but also to the fetus.

Extensive studies of the causes of fetal and neonatal deaths are being made by the Department of Obstetrics and Gynecology of the University of Chicago. From 1931 to 1938 68 per cent (526) of all infants

stillborn or dying in the neonatal period at the Chicago Lying-in Hospital have been examined at autopsy. The major causes of death are shown in Chart 1. In live born infants dying in the neonatal period there are more premature infants who die without demonstrable pathologic lesions (27.6 per cent) than there are in any other single group. (Incomplete anatomic structure and physiologic function are largely responsible for these deaths.) The remaining causes of death in order of frequency are: malformations, 24.5 per cent; hemorrhage, 23.2 per

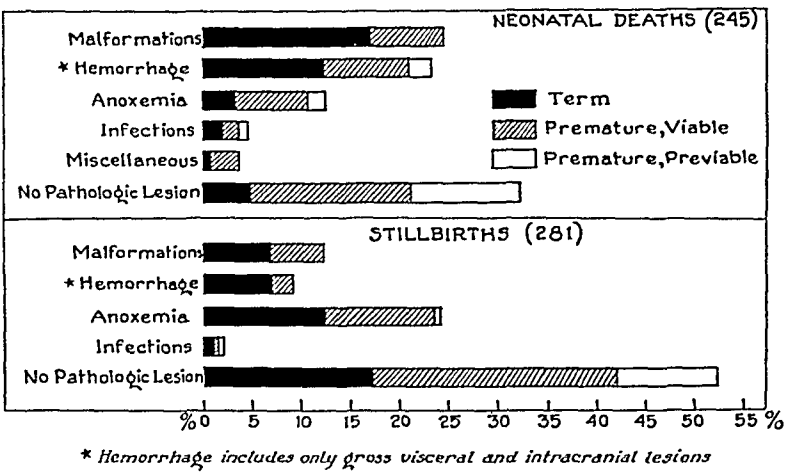


Chart 1.—Causes of fetal and neonatal deaths (526 necropsies) in the Chicago Lying-in Hospital 1931 to 1938.

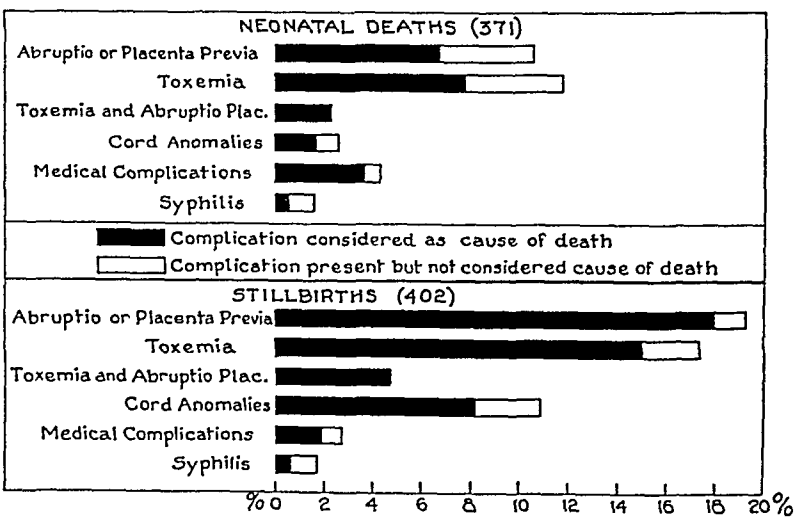


Chart 2.—Maternal complications associated with 773 fetal and neonatal deaths in the Chicago Lying-in Hospital 1931 to 1938.

cent; anoxemia, 12.2 per cent; infections, 4.4 per cent; miscellaneous, 3.6 per cent. In only 4.5 per cent of all term infants could no pathologic changes be shown. In stillborn infants the causes demonstrable by autopsy were anoxemia, 23.9 per cent; malformations, 12.4 per cent; hemorrhage, 9.2 per cent; infections, 1.9 per cent. Among the stillborn infants no pathologic changes (maceration is not included as a pathologic change) are found in a much higher percentage (52.6 per cent) of cases than among the infants dying in the neonatal period. However,

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INDUCED HYPERGLYCEMIA AT DELIVERY

Its Effect and Clinical Application

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(From the Laboratory of the Maternity Hospital, Cleveland, Ohio)

IN ORDER to fortify a patient after a prolonged labor, it has been the custom at the Maternity Hospital to administer 10 per cent dextrose intravenously just prior to delivery. During our study of the blood sugar in normal labor,[1] it occurred to one of us that the high blood sugar values thus effected in mother and newborn might approximate the levels found in diabetic patients and their infants.

The case which suggested this study was that of a primipara having a first stage of forty-eight hours' duration. She was given 500 c.c. of 10 per cent dextrose one hour and ten minutes before delivery. Immediately before the administration of dextrose her blood sugar was 122 mg. per 100 c.c.; at the moment of delivery, it was 380.4, and that of the baby was 338.8 six minutes after birth. At twelve hours of age this newborn baby had a blood sugar of 81.6, nothing having been taken by mouth.

Blood sugar values on ten cases of normal newborn infants three to six hours of age have been previously reported;[1] the values ranged from 56.9 to 79.1 mg. per 100 c.c., the mean being 66.8. It is evident that in newborn babies the slightly elevated values of birth drop to the normal infant range within a short time.

Preliminary study on three patients showed that the administration of 500 c.c. of 10 per cent dextrose intravenously within one hour of delivery produced a blood sugar level of 400 to 500 mg. per 100 c.c. immediately following the injection. Maternal values of 220, 261, and 350 mg. per 100 c.c. at delivery in these three cases seemed to be dependent upon the length of time elapsing between the injection and delivery, since the dextrose was rapidly removed from the circulating blood. Values on the infants ten to twelve minutes after birth were found to be 100 to 150 mg. per 100 c.c. higher than their respective mothers prior to the injection, indicating diffusion of the glucose to the fetus through the placenta. Within three to four hours after birth, the blood sugar values had fallen to the normal postpartum maternal and infant ranges. The data on these preliminary cases are presented in Table I.

Table I

Maternal blood sugar 1 min. before 10% dextrose	Maternal blood sugar 1 min. after 10% dextrose	Minutes between injection and delivery	Maternal blood sugar at delivery	Newborn blood sugar 10-12 min. after birth	Maternal blood sugar 3 hr. after delivery	Newborn blood sugar 3-4 hr. after birth
91.1	452.9	41	220.0	202.4		71.1
98.1	437.0	18	350.0	245.5	106.9	64.5
125.8	421.0	50	261.0	261.6	131.9	75.2

approximately half (48 per cent) of these cases showing no pathologic lesions were associated with maternal complications of which toxemia and maternal hemorrhage from placenta previa or premature separation of the placenta were the most common.

In the entire group of 773 stillbirths and neonatal deaths there was an associated complication of pregnancy or labor (exclusive of difficult or operative delivery) in 33 per cent of the live born and in 57 per cent of the stillborn infants, or in 45 per cent when both groups are considered together. In only 32 per cent, however, could the complication be considered as the probable cause of death. In the other 13 per cent definite pathologic lesions such as intracranial hemorrhage, infections, malformations, etc., were believed to take precedence over the complication as lethal factors. Chart 2 shows the incidence of the different complications in association with both fetal and neonatal deaths. It is to be noted that in only 13 of the entire group was the maternal Wassermann reaction positive and in only 4 of the infants was death believed due to syphilis.

It is evident that the persistently high fetal and neonatal mortality rates and the morbidity which is undoubtedly associated with these stationary rates present a challenge which must be met by the obstetricians. It can be met only through providing painstaking and intelligent preconceptional, prenatal, intranatal, and postnatal observation and advice. If generally and properly applied our present knowledge is sufficient to cause a gradual reduction in the fetal and neonatal morbidity and mortality to a minimum. With increasing knowledge and improvement in its application, such a minimum should in the future be further reduced by greater knowledge and its more intensive application.

SUMMARY

1. Fetal and neonatal disease and death may result from hereditary factors.

2. Environmental factors may operate upon the germ cells, embryo, and fetus prior to and during pregnancy.

3. The environmental factors occurring during the onset and course of labor are extremely important in the causation of fetal and neonatal disease and death.

4. Control of postnatal environment is especially important in preventing deaths of premature infants.

5. It is obvious from studies of results obtained in certain areas that the unchanging level of fetal and neonatal deaths can be made to decline by providing proper care for the mother, fetus and newborn infant.

blood samples taken from corresponding parts of the body in mother and infant. We have consequently been limited to micromethods using capillary blood, since this permits repeated analysis on newborn infant and mother without the complications accompanying venipuncture.

METHOD

All blood sugar estimations were made by the same person, using the Jeghers-Myers[3] modification of the Folin-Malmros ferricyanide micromethod.[4] The occurrence of high blood sugar values necessitated determination on half portions of filtrate where such values were expected as suggested by Jeghers and Myers. A

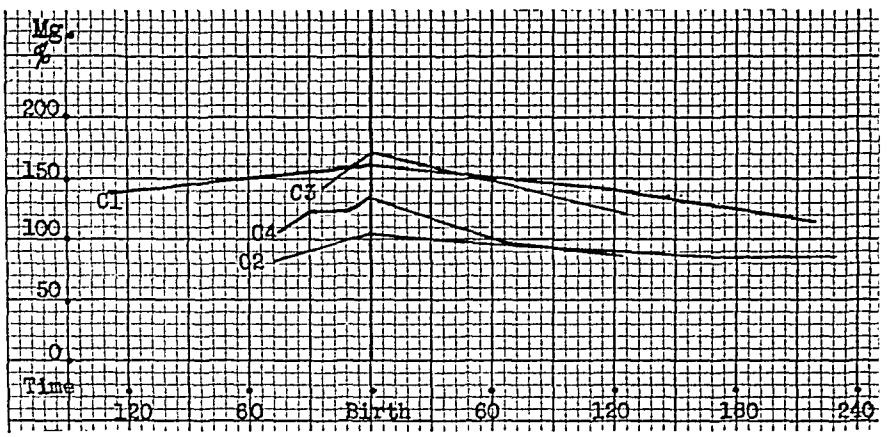


Fig. 1.—Fall in blood sugar following delivery in maternal controls.

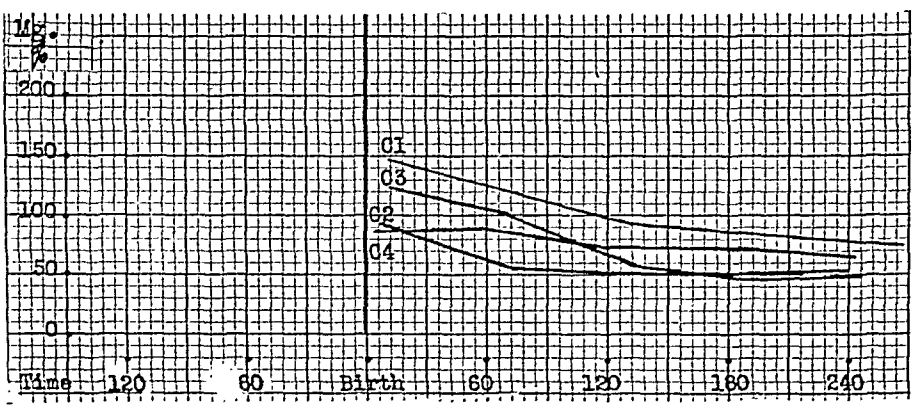


Fig. 2.—Fall in blood sugar following delivery in newborn controls.

series of standards equivalent to 70, 105, 140, 175, 210 and 280 mg. per 100 c.c. was used. When blood sugars in the range of 175 to 275 mg. per 100 c.c. were anticipated, both full and half-portions of filtrate were used. For higher values, half-portions were uniformly used and the results doubled. All colorimetric readings were made through a picric acid light filter. The final curves presented are the result of selection of the figures deemed most accurate in the range above 200 mg.; below this range no selection has been exercised. Since practically all of the infant determinations, more than 50 per cent of the maternal determinations, and all the control determinations are below 200 mg. per 100 c.c., it is evident that the curves are based for the most part on unselected data.

Delivery in normal controls and in patients having dextrose was effected by prophylactic forceps or breech extraction, and was preceded by analgesia suitable to the case. Delivery care at the Maternity Hospital has been previously summarized.[1] Data on medication and delivery are presented in Table II.

With these preliminary figures in mind, the following study was planned:

1. To administer during the second stage of labor approximately 500 c.c. of 10 per cent dextrose (50 gm.) intravenously, at a rate of 30 to 40 c.c. per minute, obtaining blood sugar values before and after such administration, samples to be taken from the hand on the side of the body opposite the site of injection.

2. To follow by hourly estimations after delivery the fall of the blood sugar in mother and newborn for the first four hours, this period being found sufficient through preliminary work.

3. To study, as a control group, several normal mothers and newborn infants by the same technique, but without having administered dextrose.

A search of the literature has revealed no similar study. Apparently very little work has been done on the blood sugar values in newborn infants. Holman and Mathieu[2] report a case of toxemia seen in consultation in which 300 c.c. of 25 per cent dextrose (75 gm.) was administered fifteen minutes prior to delivery. The blood sugar of this patient at delivery was 424 mg. per 100 c.c., and that of her infant (taken from the maternal end of the cord) was 439 mg. per 100 c.c. Apparently they did not follow the blood sugar of the infant after birth.

In a study such as this the validity of the conclusions is influenced by a number of factors. We have, therefore, attempted to hold variations in technique to a minimum. It is obvious that the concentration of the blood sugar may vary in different parts of the body following injection of large amounts of hypertonic dextrose, especially when that body is simultaneously eliminating excess glucose from the blood stream. For this reason, we feel that studies of this nature are best performed on

TABLE II. DATA ON MEDICATION AND DELIVERY

CASE	PARA	MEDICATION	BLOOD SUGAR AT DELIVERY		PRESENTATION AND DELIVERY
			MATERNAL	INFANT	
Normal Controls					
C 1	i	M & S* × 6	160.9	147.7	Breech extraction
C 2	i	M & S × 5	103.7	93.8	Podalic version, breech extraction
C 3	i	M & S × 3	170.1	121.8	R.O.A., Modified Scanzoni, low midforceps
C 4	i	None	135.5	87.0	L.O.A., Low forceps
Patients Having 500 c.c. 10 per cent Dextrose					
G 1	i	Sod. amytal gr. ix	368.5	192.3	R.O.T. to R.O.A., Low forceps
G 2	i	M & S × 3	328.8	240.6	R.O.A., Low forceps
G 3	i	M & S × 2	411.7	365.9	Low midforceps, axis traction
G 4	iv	Sod. amytal gr. ix	351.6	199.1	R.S.P., Breech extraction } Twins
				201.2	R.S.P., Breech extraction }
G 5	i	M & S × 4	277.0	226.6	R.O.A., Midforceps
G 6	i	M & S × 3	269.9	237.6	R.O.A., Low midforceps
G 7	i	M & S × 4	325.0	267.8	R.O.A., Low midforceps

*Morphine sulphate and scopolamine hydrobromide. All patients had ether analgesia and ether anesthesia.

Six of the 7 patients had blood sugar values within the normal post-partum range three to four hours following delivery.

In Fig. 4 are summarized the curves on 8 infants of mothers receiving dextrose. One infant (that of Case G 3) presented a blood sugar at delivery of 365.9, and throughout the first three hours remained higher than the group, dropping to 45.9

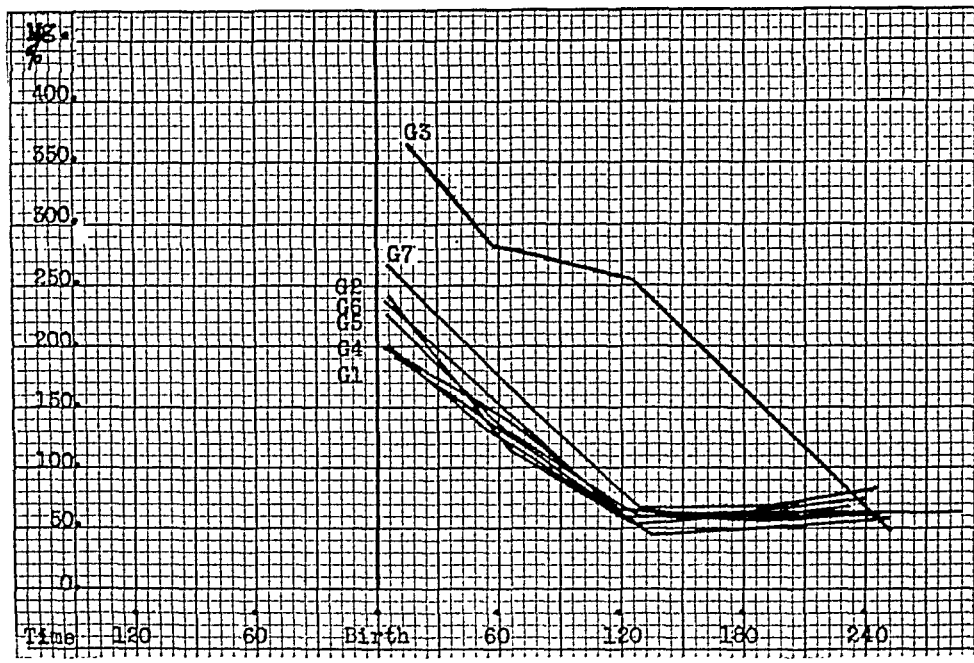


Fig. 4.—Fall in blood sugar on newborn infants of mothers receiving dextrose.



Fig. 5.—Relationship between blood sugar values of mother and her twin newborn infants when 500 c.c. of 10 per cent dextrose was administered intravenously. (Case G 4.)

ANALYSIS OF DATA

Figs. 1 and 2 show the fall in blood sugar following delivery in control mothers and infants, respectively. All the maternal and infant blood sugar values at delivery are within the normal delivery range, and there is a gradual fall to normal postpartum and newborn levels within three to four hours.

In Fig. 3 the curves for mothers having 500 c.c. of 10 per cent dextrose are summarized. Of the 7 patients, 5 attained blood sugar levels of 400 to 500 mg. per 100 c.c. Nothing in the case histories of the other two indicated the reason for the

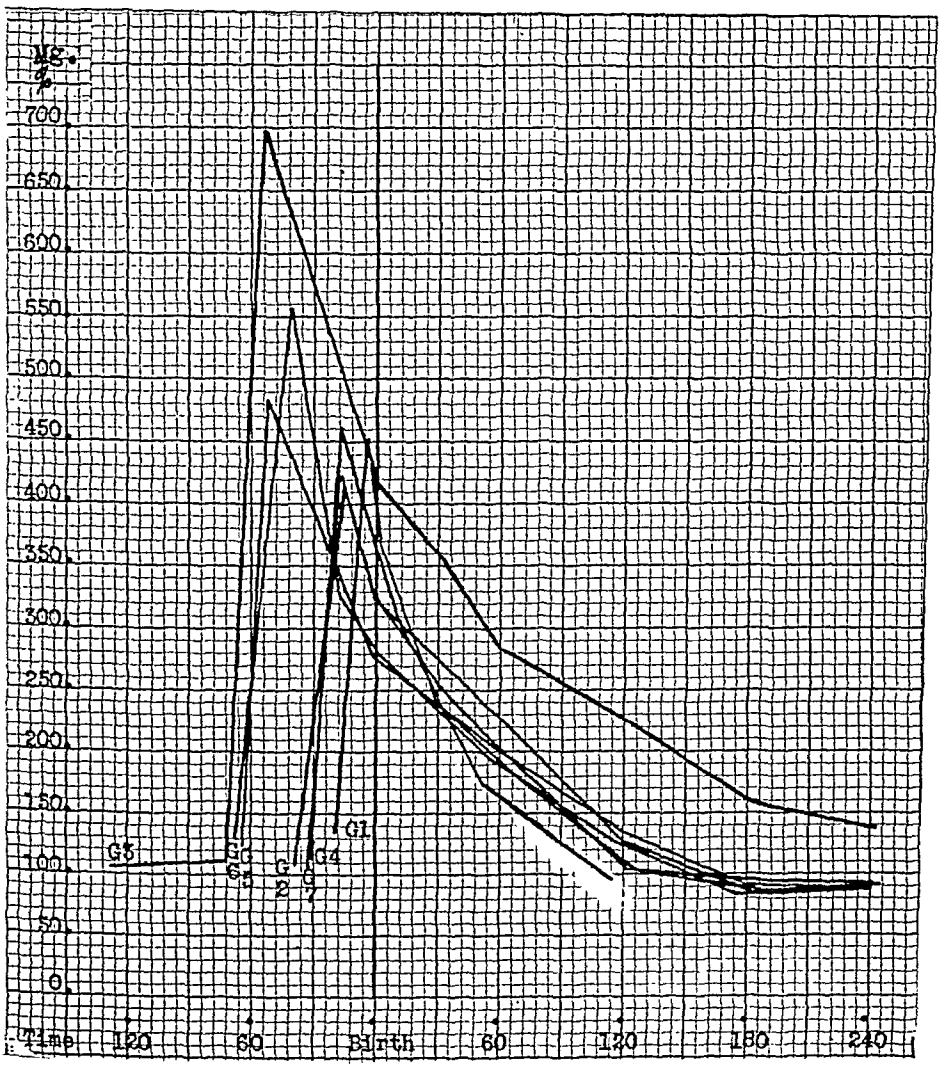


Fig. 3.—Fall in blood sugar in patients having 500 c.c. of 10 per cent dextrose.

rise to 556 to 698, respectively. Titus and Lightbody investigating the therapeutic dose of intravenous dextrose found that a small number of otherwise normal individuals respond to injections of dextrose with higher than average blood sugar values. It seems reasonable to conclude, therefore, that Case G 6 is of this type, since this curve does not show pancreatic impairment. Case G 3 might possibly be interpreted as showing slight pancreatic impairment, although detailed studies were not made. With the exception of this latter case, the blood sugar values at delivery are seen to be directly dependent upon the time elapsing between the end of administration and the moment of delivery, i.e., the closer to delivery the dextrose is administered, the higher the blood sugar at delivery. Four patients who received dextrose within thirty minutes of delivery had blood sugar values at delivery ranging from 325 to 368.5, with a mean of 341. Two others receiving dextrose more than thirty minutes before delivery had blood sugar values at delivery of 277 and 269.9.

uterine motility, it is entirely possible that when given in combination with quinine it may also increase the sensitivity of the uterine muscle to the action of quinine.

Although no attempt has been made to compare the effect of quinine-calcium with that of quinine under conditions of poor uterine motility or in animals during pregnancy, the favorable clinical reports seem to indicate that under such conditions the combination of these two products may have equally great or even greater potentiating effects.

SUMMARY

In the unanesthetized, nonpregnant rabbit, exhibiting estrin motility of the uterus, quinine-calcium produces a greater increase in uterine contractions than equivalent amounts of quinine or calcium given alone. The increase is due primarily to an increase in the amplitude of contractions, the rate remaining practically unchanged. The effect lasts for 1.0 to 1.5 hours after slow intravenous injections and for two to three hours after intramuscular injections.

NOTE.—Neo-calglucon and quinine-calcium (Sandoz) were made available through the courtesy of the Sandoz Chemical Co.

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Murphy, Douglas: Congenital Defects, J. A. M. A. 106: 457, 1936.

Married couples who become the parents of a congenitally malformed child and who contemplate having additional children, frequently inquire regarding the possibility that any subsequent offspring will also be defective. A consecutive series of 275 families, each known to have possessed a congenitally malformed or defective child and also one or more subsequent members, was interviewed with regard to the outcome of all conceptions of the mothers.

Thirty-four, or approximately 12.4 per cent, of the families gave rise to one or more additional congenitally malformed members.

Among 431 conceptions that followed the birth of the malformed child, 331, or 76.8 per cent, ended in the birth of full-term, normally developed offspring. The remaining 100, or approximately one in four of the subsequent conceptions, ended in 43 congenitally malformed children, 42 miscarriages, 9 premature births, and 6 stillbirths. In families having one congenitally malformed child, a second one was born once in every 8.9 births, whereas in the general population a congenitally malformed infant appeared only once in every 213 births.

From this study it is concluded that offspring with congenital malformations, serious enough to warrant being recorded on death certificates, is approximately twenty-four times as likely to occur in families possessing a congenitally malformed child than in the population at large.

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mg. per 100 c.c. at four hours. The other 7 infants studied showed blood sugar levels at delivery ranging from 192.3 to 267.8 with a mean of 223.6. Identical twins had blood sugar values of 199.1 and 201.2 at delivery, and values throughout the next four hours remained within 3 mg. of each other. One hour following delivery blood sugar values on these 7 infants had dropped to a range of 110 to 140. At two hours, the values ranged from 45 to 65 mg. per 100 c.c. At four hours, a slight rise to a range of 55 to 80 mg. per 100 c.c. was uniformly evident.

To show the relationship between a series of determinations on mother and infant, we present in Fig. 5 the reaction of Case G 4 and her twin infants to 500 c.c. of 10 per cent dextrose administered intravenously.

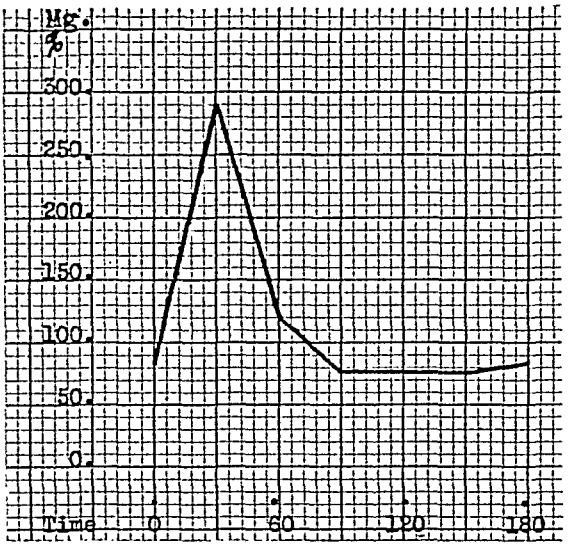


Fig. 6.—Blood sugar of normal infants after intravenous administration of 10 c.c. per pound of body weight of a 10 per cent solution of dextrose. (*Tisdall, Drake and Brown:* Am. J. Dis. Child. 30: 675, 1925.)

From a study of the data presented here, we conclude that pancreatic activity at birth is such that the blood sugar values of normal control infants and of those receiving dextrose reach normal infant levels within four hours. The slight but apparently characteristic rise occurring between the second and fourth hour in the infants receiving dextrose suggests the hypoglycemic reaction demonstrated by Tisdall, Drake and Brown[6] in slightly older infants after intravenous administration of dextrose. In their study, 10 c.c. of 10 per cent dextrose per pound of body weight caused a rise in blood sugar to 290 mg. per 100 c.c., followed in 90 to 120 minutes by a typical hypoglycemic curve, unaccompanied by clinical signs. For comparison, we reproduce the curve they obtained as Fig. 6.

The most striking feature of this work is the rapidity with which the normal infant, whatever its blood sugar value at birth, assumes the normal value for newborn infants. Factors influencing the blood sugar of the mother must be considered in the interpretation of estimations made during the first few hours of life. The unusual importance of the time element in a series of rapidly decreasing blood sugar values becomes apparent when the curves presented in Fig. 4 are carefully studied.

In turning to the clinical application of this work we have shown that it is possible to fortify not only the mother but also the premature infant, or the infant of the toxemic patient by administration of dextrose.

However, the effects of the procedure last only a few hours. In addition to its temporary nature, promiscuous use of this technique seems unjustified inasmuch as it may add considerable strain to the newborn infant already coping with the problem of adjustment to a new environment. The mother could be as adequately strengthened and any strain on the newborn infant prevented by administration earlier in labor at a physiologic rate, provided the patient's condition be such that this additional fluid load would be harmless.

We believe the clinical application of this study is to be found in the treatment of the infants of diabetic mothers. The blood sugar curves in Fig. 4 show that the pancreas of the newborn infant is as susceptible to stimulation as that of slightly older infants. These curves coincide remarkably with the work presented by Tisdall, Drake and Brown[6] on infants from one to twelve months of age, having 10 c.c. of 10 per cent dextrose per pound of body weight. Our experience with hypoglycemia in the 7 infants studied duplicates that of these workers, who showed that hypoglycemia may exist in infants without clinical signs. It seems, therefore, in caring for the newborn infants of diabetic patients that to delay until the onset of clinical signs of hypoglycemia to institute glucose therapy is to invite unnecessary, and possibly fatal, hypoglycemia. Repeated determinations of blood sugar to estimate the approximate time when hypoglycemia may be expected to occur and to guide the glucose therapy may not be practical in all cases.

The alternative to frequent blood sugar determinations is parenteral administration of dextrose at intervals. Our work and that of Tisdall, Drake and Brown[6] provides a basis for dosage and interval in such therapy. The dosage should be sufficient to put the blood sugar definitely above the hypoglycemic level, and to keep it raised for a length of time. Some workers[7] have advocated 5 to 10 c.c. of 10 per cent dextrose, which seems in the light of our work to be inadequate. Tisdall, Drake and Brown[6] demonstrated that subcutaneous administration of 5 per cent dextrose (10 c.c. per pound of body weight) caused a rise of 30 mg. per 100 c.c. in the blood sugar, while 10 and 15 per cent solutions in the same ratio caused a rise of 130 mg. per 100 c.c. In their cases, about 2 per cent of the dextrose was excreted in the urine.

Since it seems wise to avoid placing undue strain on the pancreas and liver of the infant of the diabetic patient, we suggest that the dosage of dextrose used be intermediate between these two viewpoints, namely, 10 c.c. of a 10 per cent solution per kilogram of body weight, administered subcutaneously. This amount will sustain the blood sugar for a period of two to three hours and the effects of the therapy will be evident for a longer time. The interval between administration of dextrose should be at least three hours, and preferably two to three times this long, to allow for the normal cycle of absorption, hyperglycemia, fall, hypoglycemia, and rise to fasting level. Failure to observe this time interval may result in a clinical picture obscured by pancreatic fatigue due to the constant stimulation of this organ. As soon as possible, oral feeding of karo water and formula should be substituted for parenteral administration of dextrose.

In addition to the administration of dextrose in sufficient dosage, and at proper intervals, we believe all babies of diabetic mothers should be treated as premature, regardless of weight. The constant nursing care required by prematures corresponds to that needed by the infant of the diabetic patient; it can be most simply and easily obtained by putting the infant on routine premature care. Only in this way can these newborn infants be guarded from infection, maintained at the proper temperature, and regulated in feedings without disruption of the hospital and nursery routine.

The cooperation of the laboratory service is essential. It has been found practical at the Maternity Hospital to assign a single technician to the work on diabetic patients and their infants, so that the routine of the delivery room and laboratory may proceed without disruption. When a diabetic case is anticipated, reagents and glassware are kept in readiness, and the technician is prepared to render prompt reports on urine and blood sugars.

CONCLUSIONS

1. Dextrose administered intravenously during the second stage of labor causes a definite hyperglycemia in mothers at delivery and in their infants at birth.

2. Maternal blood sugar values reach 400 to 500 mg. per 100 c.c. just after dextrose is administered and fall to normal post-partum levels three to four hours after delivery.

3. The closer to delivery dextrose is administered the higher the blood sugar values at delivery.

4. The blood sugar of newborn infants whose mothers had dextrose ranged from 192 to 267 mg. per 100 c.c. with a mean of 223.

5. There is a rapid fall in the blood sugar values of these newborn infants, resulting in a hypoglycemia which may be as low as 45 mg. per 100 c.c. followed by a slight characteristic rise.

6. Clinical application of this study is to be found in the care of newborn infants of diabetic individuals. The following are suggestions for care:

RECOMMENDATIONS FOR CARE OF NEWBORN INFANTS OF DIABETIC PATIENTS

1. Make blood sugar determination on capillary blood as soon as possible after birth, and as often as practical at intervals for the first few hours.

2. At the first indication (by laboratory findings) of hypoglycemia, 10 per cent dextrose should be administered subcutaneously in a dosage of 10 c.c. per kilogram of body weight, repeated as necessary.

3. Intervals between administration of dextrose should be at least three hours, and preferably longer.

4. Oral feedings should be instituted as soon as possible.

5. Newborn infants of diabetic patients should be placed on routine premature care, regardless of weight, since this is the most efficient way of giving these babies the constant nursing care they require.

6. Cooperation of medical, obstetrical and laboratory services is the best way of meeting the complications of diabetics and their infants.

We wish to take this opportunity to express our appreciation to Dr. Arthur H. Bill for permitting this study, and to the resident staff of the Maternity Hospital for cooperation in its execution.

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SO-CALLED LUTEIN CELL TUMORS*

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EXCLUDING the basophilic adenoma of the pituitary gland which may or may not produce Cushing's syndrome and signs of masculinization, there are two or perhaps three ovarian tumors and a suprarenal cortical tumor which produce masculinization. One of these is the arrhenoblastoma. My discussion shall be confined to the suprarenal cortical tumor and to an ovarian tumor which may be identical with the suprarenal tumor or which may be a lutein cell tumor.

The suprarenal tumors are intriguing. It seems that only malignant tumors arising in the suprarenal cortex are linked with changes in the secondary sex characteristics. If these tumors occur before puberty, they produce in both sexes precocious development and virilism (Meyer and Frumess[1]). Such a tumor came to our observation. The patient, a thirteen-year-old girl, presented typical pubertas praecox with virilism and hirsutism. At the autopsy, a carcinoma of the suprarenal cortex was found with metastases to the retroperitoneal lymph nodes and to the liver. In the mature female this tumor may produce masculinization (Cahill and co-workers[2]). Such an observation was also made by us in a 40-year-old female who presented a malignant tumor in the cortex of both suprarenals. A chromophobe adenoma of the hypophysis, perhaps an incidental finding, was also found at autopsy. In the adult male carcinoma of the suprarenal gland may rarely produce evidence of feminization (Lisser[3]). However, there are a number of instances of carcinoma of the suprarenal cortex in both sexes, which have produced no changes in the secondary sex characteristics.[2] Two such instances were also observed by us. In one of these, a kidney tumor was diagnosed clinically. In both the autopsy revealed a carcinoma arising in the suprarenal cortex.

*Presented before the Chicago Gynecological Society, October 21, 1938, as part of a Symposium on ovarian tumors.

This short survey reveals that there is a malignant tumor arising in the suprarenal cortex, a carcinoma, also called hypernephroma, which is closely linked with changes in secondary sex characteristics; most commonly pubertas praecox and virilism, if occurring before puberty, or masculinization in the adult female.

There are tumors called hypernephromas or Grawitz tumors frequently found in the kidney which are said to arise from misplaced suprarenal cortical structures. These tumors are usually bright yellow, show secondary degenerative changes and hemorrhage, and grossly and microscopically resemble those arising in the suprarenal cortex. As a matter of fact, most malignant kidney tumors are of this type. The conception of the suprarenal origin of these tumors is based upon the belief that occasionally suprarenal rests are found in the kidney, that the cells of these tumors closely resemble those seen in the suprarenal cortex and that this tumor is, as a rule, either encapsulated or seemingly well separated from the adjacent kidney structures. Not wanting to go into a discussion of what is in favor and what is against the assumption of the suprarenal origin of these kidney tumors (Saphir[4]), it may suffice to state that the mere resemblance of cells does by no means indicate a genetic relationship. This also holds for a number of so-called suprarenal rests which are said to occur quite often in the kidney. Many of these supposed suprarenal cortical rests are mere adenomas with clear cells arising from kidney tubules. The more modern conception of the so-called hypernephromas of the kidney indicates that they are carcinoma with clear cells arising, not from misplaced suprarenal cortical cells, but from similar structures such as the above-mentioned adenomas. The term hypernephroid carcinoma is merely used to denote the resemblance of these to suprarenal tumors. In favor of this conception is also the fact that, whereas the malignant cortical suprarenal tumors are in a number of instances linked with inner secretory disturbances, there is, as far as I am aware, not a single undisputed case on record where a so-called hypernephroma of the kidney, the supposed misplaced suprarenal tumor, has produced changes referable to secondary sex characteristics.

Bright yellow tumors, grossly resembling suprarenal cortical tumors and so-called hypernephromas of the kidney, also occur, though rarely, in the ovary. Descriptions of these tumors and references to other published cases are given by Glynn[5] and more recently by Schiller,[6] and Novak and Wallis.[7] These ovarian tumors are associated with masculinization and are much rarer than arrhenoblastomas. Grossly and microscopically they resemble suprarenal cortical tumors and also the so-called hypernephromas of the kidney. Like some suprarenal tumors, they produce masculinization, which may disappear after their surgical removal. On theoretical grounds and also from the morphologic and physiologic point of view, it is conceivable that these tumors actually arise from suprarenal rests. There are perhaps only three objections to this point of view. While suprarenal rests are described within the broad ligament and close to the ovary and also within the hilus of the

ovary, these rests, according to Novak and Wallis[7] are as a rule not found within the ovary itself. I myself have seen extremely few structures in the ovary which could be interpreted as misplaced suprarenal cortical tissue (Reis and Saphir[8]). This would indicate that a yellow

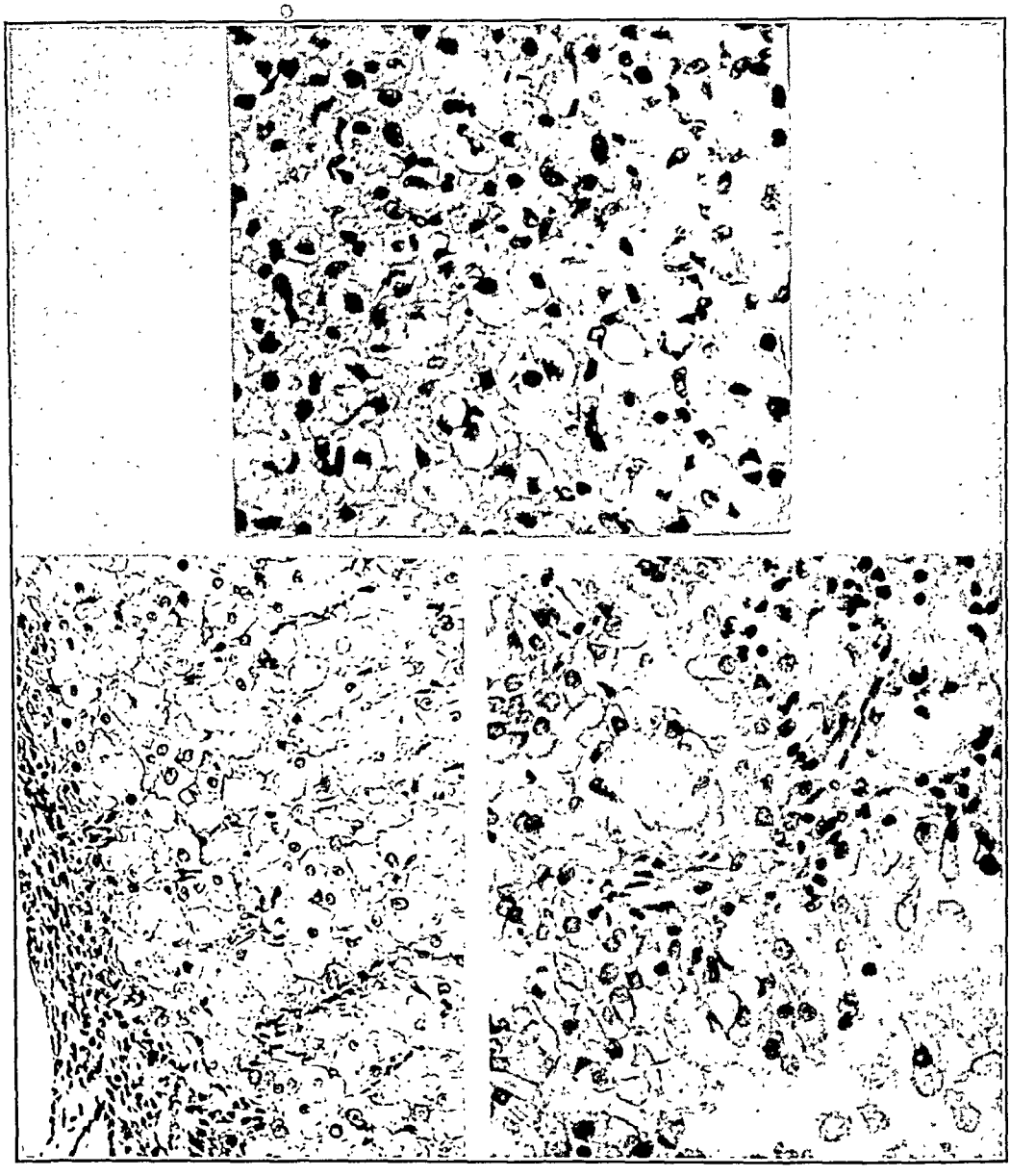


Fig. 1.—Section of yellow tumor in the ovary. (Lutein cell blastoma? Hypernephroma?) (Note the clear cells.) Iron-hematoxylin-eosin preparation; ×275.

Fig. 2.—Section of corpus luteum. (Note the resemblance of these cells to those of Figs. 1 and 3.) Iron-hematoxylin-eosin preparation; ×275.

Fig. 3.—Hypernephroid carcinoma of the kidney. (Note the resemblance of the tumor cells to cells in Figs. 1 and 2.) Hematoxylin-eosin preparation; ×275.

tumor, arising outside but close to the ovary, and which had produced changes in the secondary sex characteristics, may perhaps be interpreted as a tumor having arisen from misplaced suprarenal cortical structures. Such a tumor, of course, secondarily may invade the ovary itself. It seems extremely unlikely that a tumor of this type should arise within the ovary itself, because of the extreme rarity and doubtful occurrence

of suprarenal rests within the ovary as compared to the relative frequency of their occurrence in other locations. Another possible objection to the suprarenal origin of these ovarian tumors would be invalidated if it were actually proved that so-called hypernephromas of the kidney to which they are linked are not suprarenal tumors but true kidney tumors. If it were true that these tumors are suprarenal tumors misplaced within the kidney, just like these ovarian tumors, it would be difficult to understand why the latter should produce changes in the secondary sex characteristics and not the former. Still another argument against the assumption of the suprarenal origin of these ovarian tumors is the fact that every normal ovary normally contains cells and structures which also resemble the cells of which this yellow ovarian tumor consists, and which are possible sources of origin of this tumor. These cells and structures are lutein cells and corpora lutea, respectively. So it would seem probable that the so-called hypernephroma of the ovary is perhaps not a misplaced suprarenal cortical tumor, but a true ovarian tumor, a lutein-cell blastoma. Theoretically a tumor arising from lutein cells may give rise to masculinization because of its progesterone content. Whether such a lutein cell blastoma actually arises from corpus luteum cells or from granulosa cells which are in the process of luteinization is also very difficult to decide.

Because both the hypernephroma and lutein cell blastoma grossly and microscopically look very much alike it would seem next to impossible to differentiate these tumors histologically. Though Masson[9] claims that the latter shows a reticulum which is absent in the former, there are hypernephromas in which a reticulum is demonstrable. Since both tumors look alike, grossly and microscopically, and since both may give rise to masculinization, it is extremely likely that there is only one bright yellow tumor, arising within the ovary, which histologically consists of clear cells, resembling those seen in the suprarenal cortex and in the hypernephroid carcinomas of the kidney, and also in the corpus luteum. This tumor is closely linked to masculinization. Everything else being equal, and if one does not want to accept Cohnheim's theory without reservation, it seems safer to explain the origin of a tumor as arising from elements of the organ in question rather than from embryologically misplaced structures in that particular organ.

In the literature, there is some discussion as to the origin of these yellow ovarian tumors. In passing it may be mentioned that Schiller stated that there are only four cases which may belong to a group of masculinizing ovarian tumors and which consist predominantly of cells which store lipoids. These are the cases of Cosacesco and others,[10] Sellheim,[11] and Novak and Wallis.[7] However, Schiller[6] classified these tumors as hypernephromas and not as lutein cell blastomas, principally because they are well circumscribed and the cells in these yellow tumors are well defined, whereas granulosa-lutein cells show intercellular bridges. Further the absence of follicles in these tumors, the presence of polycythemia, hypertension and hyperglycosuria in these patients further substantiated his belief. It may be mentioned that because the

tumor appears to be well circumscribed does not necessarily indicate an origin from misplaced structures since the so-called hypernephroid carcinoma of the kidney, which probably arises from kidney structures, is also seemingly well circumscribed. The tumor which was described by Reis and myself[8] and which undoubtedly falls into this group consisted of cells which were well separated from one another and did not reveal intercellular bridges. However, this patient showed normal blood sugar and had neither polycythemia nor hypertension.

Physiologic studies with extracts of these ovarian tumors have not been made as far as I am aware, probably because of their rarity. In the future, however, it may be possible perhaps to prove the origin of these tumors and to determine whether they are lutein cell blastomas or hypernephromas. It should be possible to extract progesterone from these tumors, provided they are lutein cell blastomas, and adrenosterone, if they are true suprarenal cortical tumors. However, the differentiation between progesterone and adrenosterone may be difficult. Qualitatively there is very little difference between them (Koch[12]); quantitatively they may be differentiated. If the activity of testosterone is taken as 100 per cent the physiologic activity of adrenosterone is considered 40 per cent and that of allo-pregnandiol and pregnane, metabolic products of progesterone, as 20 to 35 per cent. Also Kendall, Wintersteiner, and Reichenstein according to Koch[13] have prepared an oxidation product from an adrenal cortical principle which is found to be one-sixth to one-fourth as active as androsterone in the capon test. So it may be possible in the future to determine the potency of extracts of these ovarian tumors and hence differentiate them by their biologic assay.

There is perhaps another way of definitely deciding whether these ovarian tumors are hypernephromas or lutein cell blastomas, and this should be tried in every instance of a yellow ovarian tumor giving rise to masculinization. Very recent experiments performed by Anderson, Haymaker and Joseph[14] have shown that the life of adrenalectomized rats may be prolonged beyond the survival periods of untreated controls if such rats are injected with benzene extracts of blood taken from patients who had the hyperadrenalo-cortical syndrome (Cushing's syndrome); the urine of one of these patients showed a similar effect. If this is true for patients with hyperadrenalo-cortical syndrome, it may very well hold for patients who have suprarenal cortical tumors, either within the suprarenal or arising in misplaced suprarenal cortical tissues. This seems evident because of the physiologic changes in all these patients. This observation of Anderson and her co-workers may be significant, in regard to the differentiation between lutein cell blastomas and hypernephromas. If benzene extracts of blood from patients suffering from such an ovarian tumor prolong life of adrenalectomized rats, it would seem that such an ovarian tumor is a hypernephroma. If this test should prove negative and on operation a yellow ovarian tumor is found, similar to the one here described, it is much more likely that this tumor then must be classified as lutein cell blastoma. Naturally this would only hold true if, first, it could be shown that progesterone

does not prolong the survival period of adrenalectomized rats, and, second, that adrenosterone, respectively cortin, is not present in corpus luteum tumors.

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DISCUSSION ON PAPERS OF DRS. KANTER, SAPHIR AND GREENHILL

DR. WALTER SCHILLER.—When one analyzes the term lutein cells from the point of view of histology, one must realize that these cells are not an entity by themselves. Such cells were not originally lutein cells but started out either as granulosa or theca cells and became luteinized secondarily; it is only then that they deserve the name lutein cells. If a luteoma is described as consisting of lutein cells there must be either theca lutein or granulosa lutein cells. They cannot be theca lutein cells, because these are a connective tissue type, while the cells of luteomas are epithelial cells. The tumor composed of theca lutein cells is the well-known xanthofibroma. In case the luteoma cells are granulosa lutein cells, two possibilities for their development are present: (a) first luteinization and second neoplastic proliferation. This means that the granulosa cell is first luteinized just as in a corpus luteum and then pathologically proliferating as in a new growth. This is not likely, since the cells of the luteinized corpus luteum are too differentiated and specialized to maintain this power of physiologic proliferation, and certainly not the capacity of neoplastic proliferation, and (b) first a neoplasm arises from granulosa cells which secondarily becomes luteinized. Such cases have been described but these tumors present a very slight degree of luteinization, not to be compared with loading of fat of the luteoma cells. Transitional phases from the poorly luteinized granulosa cell tumor to the fat-laden luteoma would prove that the latter is derived from the former but these have not been found to date. There are valid morphologic reasons against the origin of luteomas from granulosa lutein cells. Granulosa arises from mesenchyme and shows its mesenchymatous origin as long as it is not luteinized by syncytial connections of the protoplasm of the single cells which do not have distinct cell boundaries. When reaching a higher differentiation by luteinization, the single cells are still connected by fibers which pass from the protoplasm of one cell to the protoplasm of the neighboring cells. The luteinized granulosa cells do not have sharply demarcated cell boundaries, whereas the cells of the luteomas show the typical epithelial cell borders and no cell connecting fibers. In examining the luteomas for areas in which the cells do not contain fat, I have found such areas in almost all luteomas. The cells of such areas never prove the syncytial character of unluteinized granulosa cells but correspond morphologically very closely to the sharply demarcated polyhedral cells in areas of the adrenal cortex or of cortical hypernephromas in which the cells have not undergone fat storage.

DR. R. R. GREENE.—I am speaking purely as a physiologist; Dr. Schiller intimated that thecomas should not be considered as derived from the ovary, as they produce male sex hormone. I beg to state that the ovary does produce male sex hormone. Dr. Papanicolaou many years ago proved in guinea pigs that ovaries stimulated with anterior pituitary-like hormone could produce androgenic substance. In those ovaries there was a marked overgrowth of what he called interstitial tissue

which is derived from luteinized theca cells. Recently we did the same work in the rat and we got a marked growth of the clitoris. Dr. Hill about two years ago transplanted ovaries to the ears in the male rat from which the testes had been removed, and those ovaries produced sufficient androgen to keep the prostate and seminal vesicles in a normal state. To say that the ovary produces androgen does not mean it is testosterone; there are a number of androgens. As reported recently in some work at the University of Chicago and confirmed by us, progesterone in excess amounts is an androgenic substance in that it will maintain the prostate in castrated animals in normal condition. Also, progesterone given in excessive amounts to immature rats will make the clitoris grow just as with testosterone.

Dr. Kanter mentioned that there was decreased sodium in the blood and urine and said it was hard to explain. It is hard to explain how the blood sodium would be decreased but the urine sodium would be decreased due to the "sodium retaining effect of the high concentration of sex hormone."

Dr. Saphir said that testosterone is found in adrenal tumors. I believe that is not quite true. Adrenosterone has been found in adrenal tumors. This is not testosterone which is the male hormone as found in the testes. He also said that it is chemically impossible to differentiate between progesterone and testosterone. The chemical differentiation between the two with colorimetric methods or actual chemical test tube tests is not particularly difficult. The differentiation is comparatively easy in biologic assays.

Dr. Saphir also discussed the recent work of Anderson at the University of California, in which she extracted blood and urine from patients with Cushing's syndrome which she believes to be due to hyperadrenal-cortical changes, and found these extracts would maintain life in adrenalectomized rats. These patients did not show any virilizing changes; these patients did not have androgenic adrenal cortical tumors. It is difficult, then, to see how this test would be of value in differentiating ovarian and adrenal tumors.

DR. SAPHIR (closing).—The recent experiments of Anderson, Haymaker and Joseph have shown that the life of adrenalectomized rats may be prolonged beyond the survival period of untreated controls if such rats are injected with benzene extracts of blood taken from patients having hyperadrenalo-cortical syndrome (Cushing's Disease). What I meant to imply is that if this is true for patients with hyperadrenalo-cortical syndrome, it may very well hold for patients who have suprarenal cortical tumors either within the suprarenals or arising in misplaced suprarenal cortical tissues in the ovary. This may form a basis for differentiating suprarenal cortical tumors (hypernephroma) and lutein cell blastomas.

If the tumor in question arises from misplaced suprarenal cortical cells, we should expect to find adrenosterone in the tumor, which is closely related to testosterone. If the tumor in question is a lutein cell blastoma we should expect to find progesterone within the tumor. However, testosterone, adrenosterone, and progesterone are very closely related. Qualitatively there is very little difference between them, though they may be differentiated quantitatively.

DR. SCHILLER (closing).—It is a fact that the ovaries develop substances of virilizing effect and that testicles produce folliculin. What holds for physiologic tissue may be found in even a higher degree in tumors developing from it. For this reason, I think it is not safe to prove the origin of a virilizing or masculinizing tumor by its production of substances of sex influencing capacity. To classify such tumors for the time being, it is much safer to rely on morphologic criteria exclusively.

ROUTINE ROENTGEN PELVIMETRY IN 600 PRIMIPAROUS WHITE WOMEN CONSECUTIVELY DELIVERED AT TERM*

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ROENTGEN methods of pelvimetry have been in use in this clinic for a considerable period and during the past four years we have employed these methods routinely in primiparous patients. Early in 1937 I[1] reported our findings in the first 300 white women in whom this routine was carried out and later in the same year[2] the results in 450 white women were published. It is our opinion that the value of roentgen pelvimetric methods may be demonstrated best by the study of a group of women consecutively delivered at term (child 2500 gm. or over) in whom the influences of race, multiparity, and premature birth are not present. Obviously, it is the primiparous woman who should derive the greatest benefit from the knowledge of the true size and conformation of the bony pelvis. Furthermore, the conduct of labor in such patients will always remain one of the chief concerns of the obstetrician.

The present studies are based on the findings in 600 white primiparous women consecutively delivered at term in the wards of New Haven Hospital in whom roentgenometry of the pelvis has formed part of the routine prenatal program.† I propose to discuss in particular some of the problems of labor in this group and to point out the aid that such roentgenometric methods have given us. I shall consider only briefly the variations of the pelvis which we classify according to the dimensions found at the superior strait as follows:

Dolichopellic type: The anteroposterior diameter is longer than the transverse. In appearance the pelvic inlet is elongated anteroposteriorly.

Mesatipellic type: The anteroposterior and transverse diameter are of equal length or the anteroposterior diameter is slightly shorter than the transverse (never more than 1 cm.). In appearance the pelvic inlet is round.

Brachypellic type: The anteroposterior diameter is 1 to 3 cm. shorter than the transverse. In appearance the pelvic inlet is elongated transversely.

Platypellic type: The anteroposterior diameter is 3 cm. or more shorter than the transverse. The pelvic inlet is definitely flattened in its anteroposterior aspect.

When pelvic characters generally known as android changes, including narrowed forepart, funnel outlet, narrowed notch, etc., are present, such changes are noted in association with the above. In addition, we subdivide each of the above groups into large, average, and small pelves. Those interested in this complete classification are referred to one of my articles.[3] It is our feeling that the use of the terms dolichopellic, mesatipellic, etc., is more correct and more useful as a basis for the classification of pelvic variations than terms which may suggest etiologic factors concerning which we know so little.

*This study was made possible through the Research Funds of Yale University School of Medicine.

†In a few instances patients to whom no prenatal care has been given by us have entered our wards far advanced in labor. In such cases roentgenometry was carried out before the patient left the hospital. The number of those cases represents less than 1 per cent of the entire series.

negative. The absence of ureteral dilatation, as demonstrated roentgenographically in Fig. 2, was verified by post-mortem gross and microscopic examination.

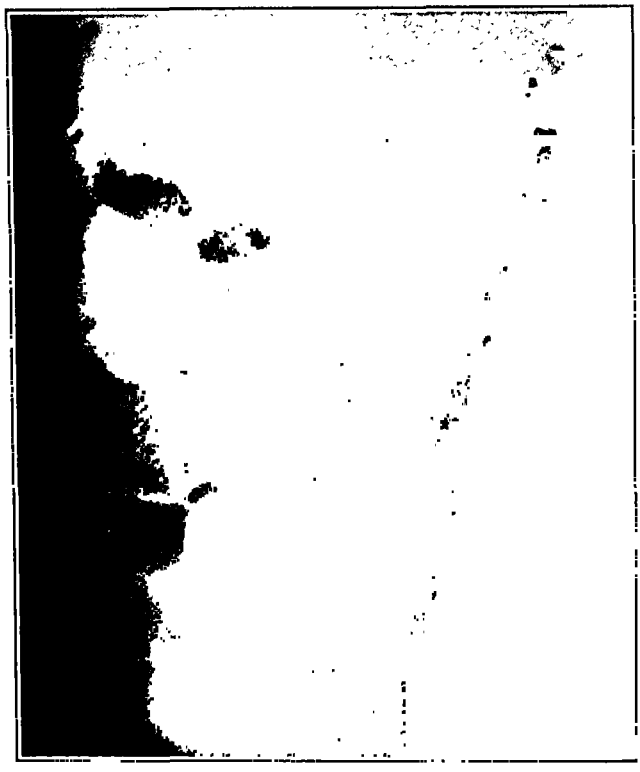


Fig. 2.—Urogram of rabbit which had received 20 I.U. of progesterone. No ureteral dilatation.

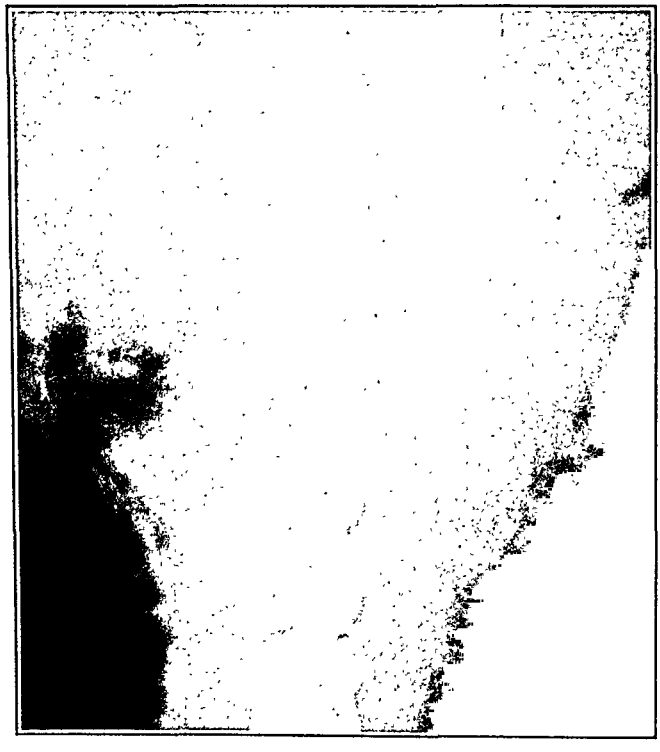


Fig. 3.—Urogram of a dog in the seventh week of gestation. No ureteral dilatation.

and 10 c.c. in dogs. Injections were made into a leg vein in the dogs and into an ear vein in the rabbits, with no attempt to prolong the period of introduction. In spite of this, no untoward reactions were noticed. At completion of the injections, the animals were fixed upon a board in the supine posture and immediately placed in an extreme Trendelenburg position with the plane of the board sixty degrees to the horizontal. The physical factors employed were as follows: 100 ma.; 60 to 70 kv; 1/15 to 1/20 second; 30-inch target film distance. A fine focus rotating anode tube and casettes with double intensifying screens were used.

During the early period of these studies, each animal was radiographed at four-, seven-, ten-, and fifteen-minute intervals. More recently, only the seven- and ten-minute examinations were made, as it was found that the four- and fifteen-minute exposures added nothing to the urographic study.



Fig. 1.—Urogram of dog after 44,000 B.D.U. of pregnancy prolan. No ureteral dilatation.

The excellent visualization of the upper urinary tract which resulted from this method made it unnecessary to resort to abdominal compression or purgation[7] in order to obtain satisfactory renal and ureteral detail.

The results obtained on dogs and rabbits following injections of pregnancy prolan are tabulated in Table I. Urograms, which were made at intervals of seven to ten days (Fig. 1), revealed no evidence of ureteral dilatation. Sections through the upper, middle, and lower portions of the ureters revealed no significant deviation from the normal.

Injections of estrin also failed to produce ureteral dilatation (Table II). Urograms were obtained at intervals of fifteen days during the experiment and subsequent microscopic study of the ureters confirmed the x-ray findings.

Twenty international units of progesterone were injected into each of two rabbits over a period of twenty days. The results, which are tabulated in Table III, were

SUMMARY

1. A method for obtaining intravenous urograms in lower animals is described.

2. Attempts to produce ureteral dilatation in rabbits and dogs by hormone injections have been unsuccessful.

3. Urographic examinations of pregnant dogs and rabbits have revealed no evidence of ureteral dilatation.

We wish to express our gratitude to Drs. F. E. Keene and E. P. Pendergrass for their continued interest during this study. We are also indebted to the following contributors: Research Department, Winthrop Chemical Company for a generous supply of diodrast; Ayerst, McKenna and Harrison for an ample quantity of anterior pituitary-like hormone; Schering Corporation for an adequate amount of progynon B.

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THE POSTMATURE FETUS*

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THE postmature fetus may be defined as an overdeveloped fetus near or beyond term or any fetus born well beyond the expected date of labor.

I have gone over the histories of all large babies weighing 9 pounds (4072 gm.) or more delivered at The Brooklyn Hospital from 1935 to 1937 inclusive, in an effort to determine the risk involved to the mother and fetus.

TABLE I. DELIVERIES 1935 TO 1937 INCLUSIVE

		FETAL MORTALITY (UNCORRECTED)		FETAL MORTALITY (CORRECTED)
Total deliveries	3314	160	4.83%	2.03%
Group I (9 to 10 pounds)	157	6	3.82%	3.18%
Group II (10 pounds and over)	30	4	13.33%	13.33%

During this period, 3,314 babies were delivered. There were 160 stillbirths and neonatal deaths. The corrected fetal mortality was 2.03 per cent.

Those weighing 9 pounds (4072 gm.) or more were classified as postmature from the standpoint of development. Of these, there were 187 which were divided into two classes.

Group I weighed between 9 and 10 pounds, of which there were 157, and 6 babies were lost. The corrected fetal mortality was 3.18 per cent which is about 50 per cent higher than for the entire series. No further analysis was made of this group

*Read at a meeting of the Brooklyn Gynecological Society, November 4, 1938.

TABLE I. EFFECT OF PREGNANCY PROLAN

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Dog 25	22	44,000 B.D.U.*	44 Days	5	No dilatation
Dog 528	22	44,000 B.D.U.	44 Days	5	No dilatation
Rab. 4	6	1,350 B.D.U.	14 Days	2	No dilatation
Rab. 5	6	1,350 B.D.U.	14 Days	2	No dilatation
Rab. 6	9	9,000 B.D.U.	20 Days	2	No dilatation
Rab. 7	9	9,000 B.D.U.	20 Days	2	No dilatation

*B. D. U., Biologic day units.

TABLE II. EFFECT OF ESTRIN

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Dog 25	9	18,000 R.U.	47 Days	3	No dilatation
Dog 528	9	18,000 R.U.	47 Days	3	No dilatation

TABLE III. EFFECT OF PROGESTERONE

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Rab. 10	4	20 I.U.	20 Days	2	No dilatation
Rab. 11	4	20 I.U.	20 Days	2	No dilatation

The effect of pregnancy has been studied previously by Mengert,[6] who reported that examination of post-mortem specimens disclosed no appreciable differences between the ureters of pregnant and nonpregnant lower animals. Our urographic studies in six pregnant animals, which are summarized in Table IV, support Mengert's findings. Since the average period of gestation is sixty days in dogs and thirty days in rabbits, it is obvious that the pregnancies were well advanced at the time of the urographic examinations. Fig. 3, showing no ureteral dilatation, is that of a dog in the sixth week of gestation.

COMMENT

The number of experiments included in each group is too small to be of statistical importance. The uniformly negative results, however, seem to indicate that the hormones which were injected are not capable of producing ureteral changes in dogs and rabbits. It is possible that insufficient quantities of these agents were used or that sufficient time did not elapse between the first injection and the last urogram. Since ureteral dilatation does not occur during pregnancy in dogs or rabbits, it is unlikely that this change can be produced in these animals by any type, or combination, of hormone medication.

TABLE IV. EFFECT OF NORMAL PREGNANCY

ANIMAL	LENGTH OF PREGNANCY	UROGRAM
Dog 384	6 Weeks	No dilatation
Dog 368	7 Weeks	No dilatation
Dog 519	6 Weeks	No dilatation
Dog 695	Well advanced	No dilatation
Rab. 8	3 Weeks	No dilatation
Rab. 9	3 Weeks	No dilatation

theoretically due Feb. 8. Labor started spontaneously and lasted five hours and twenty-six minutes. The vertex was delivered by manual control and the shoulders were delivered with difficulty by the Kristeller method. The fetal heart was present shortly before delivery. The baby weighed 10 pounds 2½ ounces. An autopsy revealed no apparent cause of death.

A 32-year-old, para i, with an ample pelvis had a spontaneous onset of labor and was delivered ten days after her expected date. After twenty-one hours of labor, the vertex was easily delivered by low forceps. Difficulty was encountered in the delivery of the shoulders, rotation of which was unsuccessful. They were finally delivered by pressure on the fundus. The fetal heart was present before delivery. Death was thought to be due to asphyxia caused by delay in shoulder delivery.

A 34-year-old, para iii, with an ample pelvis had two previous children weighing 9 pounds 7 ounces and 11 pounds 12 ounces, born alive and well. Labor started spontaneously in the L.O.A. position, and the vertex was delivered by manual control twenty-six hours and forty-two minutes after the onset. The shoulders were delivered with difficulty after giving 1 c.c. of pituitrin and using considerable pressure on the fundus. An autopsy showed no apparent cause of death of fetus which weighed 10 pounds 8 ounces.

A 37-year-old, para iii, had two previous babies weighing 11 pounds and 9 pounds were alive and well. Labor was induced by castor oil and quinine, the position being R.O.P. The first stage of labor lasted only three hours, but the pains were very severe; the duration of the second stage, one hour. The delivery was spontaneous. The baby weighed 10 pounds 8 ounces and lived two hours. An autopsy showed laceration of the tentorium cerebelli with hemorrhage.

The etiology of the postmature fetus has been attributed to various factors, such as a familial tendency involving either the mother or father or both. Diet and lack of exercise are considered factors by some. It is commonly stated that multiparas and elderly primiparas are more likely to have large babies. In view of our present knowledge, the postmature fetus resulting from prolonged pregnancy may be due to a hormonal imbalance.

Koff and Davis[1] studied the mechanism of the prolongation of pregnancy in the rabbit and concluded that the corpus luteum hormone or progestin is directly responsible for the maintenance of pregnancy in the rabbit and its normal termination. By injecting pregnancy urine extract to form new corpora lutea or by repeated injections of progestin, they were able to prolong the duration of pregnancy in the rabbit well beyond the customary thirty-two days. When pregnancy was thus prolonged, large postmature fetuses were produced, and, if delivered before the thirty-sixth day, they were alive and normal; if, however, delivered after this date, many of them were dead. Those that survived were large, obviously postmature; the labor was unduly prolonged, sometimes lasting forty-eight to seventy-two hours. They state that this may be due to the excessive size of the offspring but the effect of progestin in diminishing the irritability of the contractile powers of the uterine muscles also may be a factor.

If we are willing to accept that the delivery of a postmature fetus carries a relatively high fetal mortality and possibly a high maternal morbidity, the importance of diagnosing this condition before it has advanced too far is evident. As a guide, we should obtain an accurate history of the last menstrual date. If the patient gives a history of irregular time of menses, especially with periods of amenorrhea, not too much importance can then be attached to the date of the last menstruation. The date of quickening may be of value. Knowledge that the husband is large and a history of previous large babies, should be

other than noting that three sections were done which practically corresponds to the average number of sections done for the whole three-year series.

Group II included all babies weighing 10 pounds (4,800 gm.) or more, the analysis of which is given in greater detail. Thirty babies were delivered in this series with a fetal mortality of 4, or 13.33 per cent. This much higher mortality was found to be due mainly to the difficulty encountered in the delivery of the shoulders. There were 18 multiparas with an average labor of eight hours and twenty-seven minutes. The 12 primiparas had an average labor of twenty-three hours and twelve minutes. The presentations were vertex, of which 13 were posterior, two were transverse and 15 were anterior. The pelvic measurements were classified as ample in 26 and no classification given in 4.

TABLE II. GROUP II. BABIES WEIGHING 10 POUNDS OR MORE

	PREMATURE	POSTMATURE	EXPECTED DATE NOT RECORDED
Less than 1 week	5	5	3
1-2 weeks	2	6	
2-3 weeks	2	5	
3-4 weeks	1	0	
5-6 weeks	0	1	

From the menstrual history 17 were overdue; one patient went thirty-six days beyond her expected time and her baby weighed 10 pounds 14½ ounces. Accurate data were not obtained in three patients. Ten delivered before the expected date; one of these delivered twenty-three days early, and the baby weighed 10 pounds 3½ ounces. Labor was induced by castor oil and quinine in 4. The others had a spontaneous onset. Practically all patients received morphine and scopolamine for seminarcosis. In addition some received ether, oil and quinine per rectum.

TABLE III. GROUP II. MODE OF DELIVERY

Cesarean section	2
Midforceps preceded by manual rotation	2
Midforceps	1
Low forceps	3
Perineal forceps	7
Spontaneous	15

Two cesarean sections were done on 2 primiparas following a test of labor. Two babies presenting in the posterior position were converted into anterior position by manual rotation of 180 degrees during the first stage and midforceps extraction was required at a later time in both. Four other cases required extraction, three low forceps and one midforceps. Seven were delivered by forceps control and 15 babies were born spontaneously. Episiotomies were done on 14; first-degree lacerations occurred in 4; second-degree lacerations in 6; 4 had no lacerations. There were 3 female infants and 27 male infants. The relatively large number of male babies in this small series may be a coincidence but the preponderance of male babies in the postmature class has been noted by others. Twenty-five of these patients were service cases and 5 were private. The service deliveries in our hospital usually run a little more than half of the total deliveries. Overeating and lack of exercise have been thought by some to be the cause of overdevelopment of the fetus. It is possible that proper diet and exercise were stressed and more faithfully carried out by the more intelligent private patients, with fewer postmature babies resulting. There were 2 post-partum complications: hemorrhage and a mild phlebitis. During convalescence no patient developed a reportable fever. Twenty-six babies were discharged in good condition. The following is a short summary of 3 stillbirths and a neonatal death:

A 30-year-old, para iii, with an ample pelvis had had two previous labors, both babies weighing over 8 pounds. This baby was born Feb. 5, 1935, and she was

COMMENT

The high fetal mortality in this small series was due mainly to difficulty encountered in the delivery of the shoulders.

When the delivery of a large baby is suspected competent assistance should be present in order to manage properly the delivery of the shoulders.

None of these babies died directly as a result of prolongation of pregnancy as they were all alive just prior to delivery.

The average duration of labor was prolonged.

Maternal morbidity was not high and no serious maternal complications occurred.

Induction of labor may occasionally be justified for prolonged pregnancy resulting in an overdeveloped fetus but each case should be carefully individualized before it is attempted.

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DIABETES IN PREGNANCY WITH OBSERVATIONS IN 28 CASES*

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INSULIN has made pregnancy relatively safe for the diabetic mother. On the other hand, it has complicated the problem because we now see patients with severe diabetes, who in the pre-insulin era would never have been pregnant. Furthermore, insulin has led the practitioner into a false sense of security and this undoubtedly has been the cause of some maternal and many fetal deaths. There are several aspects of this problem which warrant discussion.

1. SAFETY OF MOTHER

In the past five years we have had 28 pregnant diabetic women at the Jewish Hospital. No mothers were lost.

It may be stated that a maternal death from diabetes requires proof that this death was not avoidable. Whereas even in the best of hands such an accident may occur, it should be rare. Joslin has been able to report 73 pregnancies without a maternal death from diabetes, even though 22 of his cases were in total diabetics.

The price for this maternal safety is close collaboration between the obstetrician and the diabetic specialist. Few obstetricians are capable of handling such a problem without help.

*Read at a meeting of the Brooklyn Gynecological Society, November 4, 1938.

noted. Before the diagnosis of a large baby is made, the following should be excluded: twin pregnancy, hydramnios, and pregnancy complicated by tumors. If doubt exists regarding the relative size of the baby after careful abdominal and bimanual palpation, the following measures have been advocated as valuable aids: roentgenograms, cephalometry and mensuration in utero.

The treatment should vary with the individual case. If there is an obvious disproportion, a cesarean section should be done. If it is felt that delivery is possible through the natural passages, induction of labor is advocated by the authors[2-5] whom I have reviewed.

Various methods for induction have been advocated, such as the following: castor oil, quinine, pituitrin, either subcutaneously or intranasally, rupture of the membranes, stripping of the membranes, insertion of a bougie or a bag. Frequently, a combination of these methods is used.

When doubt exists about delivery through the natural passages, radical measures for induction should be avoided so that a section can be done with less risk to the mother should the necessity arrive.

During labor, the patient should receive proper supportive measures. If we are dealing with slow progress in an occipitoposterior position, a rotation of 180 degrees to convert it into an anterior position on the opposite side, in the same oblique diagonal, often hastens the progress of labor with less fetal trauma and simplifies the application of forceps, should it become necessary. Delivery of the shoulders of very large babies is frequently a problem as shown by our mortality. Spontaneous delivery of the vertex is desirable under gas-oxygen analgesia, as this will not interfere with the proper bearing-down pains that are so necessary to deliver the shoulders. Should the pains be insufficient after the head is born, three or four minims of pituitrin may be tried. When forceps has been used to deliver the head and the patient is under a general anesthetic, proper and forceful pressure on the fundus will often deliver the shoulders. Traction on the baby's head should be avoided, as this may readily cause damage to the brachial nerve plexus or spinal cord. Titus describes the following valuable method of the delivery of the shoulders. Between pains insert two or three fingers into the vagina behind the lower shoulder and rotate the axis of the shoulders into the nearest oblique diameter of the pelvis. As the next uterine contraction occurs, traction is made by the fingers in the posterior axilla, pressure is made above the symphysis pubis by the external hand to engage the anterior shoulder, while the nurse or assistant presses firmly downward over the contracted fundus. The pressure should not be made between pains as it is ineffective when not reinforcing a uterine contraction. Moreover, this might cause placental separation. If this fails, the remainder of the examining hand is inserted into the vagina, is passed forward over the shoulder and chest and the posterior arm thus delivered. It is usually flexed at the elbow, and as the hand often comes into view early, it may be grasped, drawn upward and out and the arm delivered by its extention through traction on the arm.

it likely that the cause of the high incidence of toxemia in diabetic women lies in the pituitary.

5. HYPERINSULINISM OF INFANT

It is believed that the baby borne by the diabetic mother may secrete an increased amount of insulin and this may cause hypoglycemia and convulsions in the first few days of postnatal life. Many authors recommend early feeding of dextrose and even intramuscular injection of 10 per cent glucose to prevent hypoglycemia and its consequences.

6. DELIVERY

Within recent years, several authors have advocated cesarean section before term to prevent death in utero. They advise, when the fetus is sufficiently large, to deliver it by section. Such advice is open to question. I do not believe that the number of babies lost by awaiting labor and delivery warrants this radical step. One author reports that three babies died in a series of 14 patients in whom he performed cesarean section to prevent fetal death. Surely it cannot be pleasant to do a section for a fetal indication and then lose the baby from whatever cause.

In these days, when cesarean section is being done for more and more indications, we should hesitate before adding another indication. Cesarean section is still a dangerous operation and diabetes does not render it less so.

Cesarean section was performed twice in our series. In one case, the indication was cephalopelvic disproportion. In the second case, section was done one month before term because of four previous stillbirths.

It is my opinion that the diabetic patient should be delivered per vagina. If the baby is large and it appears that delivery will be difficult, then cesarean section should be resorted to. In the rare case in which the diabetes cannot be controlled and the condition fluctuates between acidosis and hypoglycemia, section should be done as soon as the fetus is viable and the tubes should be ligated.

Labor must be conducted with extreme care. The diabetic specialist should be in constant attendance. Hourly blood sugar determinations should be made and the urine watched closely for acetone; and treatment should be based upon these findings.

Morphine should be used as an analgesic rather than the barbiturates or rectal ether.

7. THERAPEUTIC ABORTION

Therapeutic abortion was performed four times in our series. In retrospect, the reader believes that this was not always indicated.

Therapeutic abortion is seldom indicated in the diabetic patient today. In the severe case of hyperemesis in which control of the diabetes is impossible, abortion is indicated. There is also the rare case of severe diabetes which becomes worse as pregnancy progresses

The status of the diabetes changes with the progress of pregnancy and requires constant checking to prevent the development of acidosis and coma. Hyperemesis, with the resultant derangement of metabolism, may tax the skill of the trained diabetic specialist if tragedy is to be avoided. The alimentary and renal glycosuria which are so prone to develop after the middle of pregnancy further complicate the problem. The fetal demands and increased nutritional needs of the end of pregnancy again make control a delicate problem. The old teaching that the development of the fetal pancreas renders the maternal diabetes milder, is not accepted today. Usually the carbohydrate tolerance diminishes as pregnancy progresses. It has been my experience that the insulin requirements increase as pregnancy advances.

2. SAFETY OF BABY

We had four stillbirths in our series. Two of them occurred in cases in which the diabetes was not discovered until glucose tolerance tests were done post partum. One occurred in a case in which the mother refused to follow the outlined therapy. The fourth stillborn infant weighed 11 pounds 15 ounces and died as a result of difficult delivery. Of course, a cesarean should have been performed in this case.

Death of the fetus in utero near the end of pregnancy still occurs occasionally, in spite of all care. Although this accident cannot always be prevented, it is our experience in Brooklyn that vigilance in the care of the mother will reduce its incidence greatly. Hospitalization at the end of pregnancy will undoubtedly prevent many fetal deaths.

3. SIZE OF BABY

Six babies in our series weighed over 9 pounds. The oversized baby of the diabetic woman is well known to obstetricians. It is my opinion that careful control of the diabetes greatly reduces the frequency of large babies. Although there is some difference of opinion, most students of the subject believe that careful control of the diabetes will in most cases insure a live baby of normal size.

It is interesting to speculate here on the cause of this overgrowth of the fetus. The old theory that the overgrowth is due to the abundant food supply (hyperglycemia and lipemia) is now challenged by White. This author believes that it may be caused by the pituitary. The high incidence of toxemia in diabetes, the high prolan in toxemia, and the work of Snyder and Hoopes, who injected prolan into pregnant animals to prolong pregnancy and produce oversized offspring, are neatly joined in a theory to attribute the overgrowth of the fetus to the pituitary. This theory seems plausible, and it will be interesting to see whether further studies bear it out.

4. TOXEMIA

The work of Smith and Smith, who showed high prolan content in toxemias, and the fact that the pituitary is involved in diabetes, make

OCCURRENCE OF PELVIC VARIATIONS

In this group of 600 white women variations according to the above types occurred as follows:

Dolichopellic type,	92 instances	or 15.3 per cent
Mesatipellic type,	272 instances	or 45.3 per cent
Brachypellic type,	210 instances	or 35.0 per cent
Platypellic type,	26 instances	or 4.3 per cent

As in previous reports the mesatipellic or round pelvis predominates (approximately one-half of the series) while the brachypellic or transversely elongated type (oval) occurs in about one-third of the series. This commands interest in view of the fact that until very recently most textbooks held this latter type to be representative of the normal female pelvis. I have discussed certain aspects of this question in an article entitled "What Is a Normal Pelvis?"[4] At this time I may add that from a pragmatic point of view it is reasonable to assume that nature intended the round fetal head (suboccipitobregmatic circumference) to be adapted to a round and not oval-shaped pelvic inlet. In the present communication both the occurrence of variations and the clinical findings associated with the various groups tend to bear out this concept.

It is pertinent to discuss briefly the procedures which we use in a pelvimetric survey of the pelvis:

First: A roentgenogram of the superior strait is made using the so-called "Grid" method.[5] This shows the complete outline of the superior strait and the diameters of this plane may be read directly from the film by means of the corrected centimeter dots appearing on the film. Furthermore, such roentgenograms allow exact reduction of the outline of the superior strait to true centimeters. This record is filed with the prenatal record and is, therefore, immediately available at whatever hour the patient may enter the hospital. These reduced and true images on centimeter paper have a further advantage in that the superior strait is visualized in its true size, not as an enlarged image as it is viewed in the film. In addition this view also allows the mensuration of the important bispinous diameter using a table which corrects for the divergence of the roentgen rays at the level in which these processes rest. This level is ascertained by viewing the lateral film.

Second: A lateral roentgenogram is obtained using a technic described by Thoms and Wilson.[6] In this procedure the patient stands upright with the lateral body plane toward the target at a target film distance of five feet. Resting in the buttocks fold in the midplane of the body is a vertical opaque centimeter notched rod the shadow of which on the film forms a scale for correcting distortion due to the spread of the rays. Views taken in this manner depict all the anteroposterior diameters of the pelvis including the anterior and posterior sagittal diameters of the narrow pelvic plane and the pelvic outlet, the contour and position of the sacrum, and the character of the sacrosciatic notch. This lateral technic used at term or in labor is eminently useful in showing the size and station of the fetal head in its relationship to the bony birth canal. In trial labor this procedure appears to be of exceptional importance.

Third: External pelvimetry of the outlet is done employing the methods described in Williams-Stander and other textbooks.

Emphasis should be made upon the simplicity of the roentgen methods employed. They require but one 10 inch by 12 inch film for each view and, therefore, reduce the cost per patient to a minimum. In appraising the value of roentgen pelvimetric methods in obstetric procedure, the author has recently stated: "The usefulness of the knowledge of the

and control cannot be maintained. In this case, termination of pregnancy is indicated to save the mother's life. Fortunately, this is seldom necessary.

8. ANESTHESIA

For delivery per vaginam, local infiltration or pudendal block is the anesthesia of choice. For cesarean section, local infiltration is safer than general or spinal anesthesia.

9. CONCLUSIONS

1. Death of the fetus near term can usually be prevented.
2. Adequate care will usually prevent an oversized baby.
3. Death of the mother should be rare.
4. Cesarean section is warranted only for special indications.
5. Therapeutic abortion is seldom indicated.

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BILATERAL SIMULTANEOUS TUBAL PREGNANCY

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A REVIEW of bilateral simultaneous tubal pregnancy cases uncovers a number with insufficient data for classification. Aside from the clinical facts given in reports there should be a description of the fetuses or any portion of them found, as well as of placental material. A microscopic examination may be necessary to confirm the diagnosis and to give criteria for fixing the pregnancy periods. Especially is this needed where only a hematosalpinx is present grossly. Fetal structures recently dead may give dependable findings,[1] but badly degenerated tissues or mummified or calcified products are of little value in estimating the time factor.

Many of the cases were found in journals of limited circulation, and probably others have been missed because of inaccessibility. Those presented in earlier reviews have been gone over with the above criteria in mind and acceptable ones are included here.

The review by Jayle and Nandrot (1904)[2] includes two acceptable cases, one each of Johnson, and of Jayle and Nandrot. Labhardt (1909)[3] adds seven more cases. Five new cases are added by Launay and Seguinot (1911),[4] and two by Unterberger (1913).[5] The subject was considered at length by Bledsoe (1918)[6] with the presentation of 24 new actual or highly probable cases. Borell (1921)[7] found 9 more. A thesis by Bloch (1931)[8] presents 11 additional cases. Another case, the third case of Penot, is found in the review of von Kupercyn (1932).[9]

Other cases, not discussed in the foregoing reviews, will be named here without discussion. Lockyer (1916),[10] Jordan and Bigger (1925),[11] Dalzell (1927),[12] Schockaert (1928),[13] two cases of Nevinny (1929),[14] Heymann (1932),[15] Johnston (1932),[16] Cramarossa (1934),[17] Stahel (1934),[18] Langley (1934),[19] Léon-Borcéa (1935),[20] Siegler (1935),[21] Corceovei and Corceovei (1935),[22] and Muller (1935).[23]

The entire group represents 76 cases of bilateral simultaneous tubal pregnancy, reviewed in the light of the principles for acceptance discussed earlier. To these I should like to add a further case. This patient was proved to have 3 simultaneous tubal pregnancies, 2 in the left and 1 in the right tube. Only 2 similar cases have been found reported previously, 1 by Launay and Seguinot (1911),[4] and the second by Baldwin (1913).[24]

CASE REPORT

Patient H. C., aged 32 years. In seven years increased from 145 to 227 pounds in body weight. She was married and had had three spontaneous abortions; no living children. Menses were regular and normal except during her pregnancies. Last regular period was twelve weeks before entry into hospital. Almost daily spotting for the last four weeks, and for two weeks this was accompanied by vague lower abdominal pains. On the day of entrance, she was seized with sudden sharp cramplike pains in the lower abdomen, and shortly thereafter passed a small amount of blood vaginally. Several hours later she had a second attack of similar acute abdominal pain and was brought to the hospital in a shocklike state and was operated upon.

A massive hemorrhage was found in the peritoneal cavity. The left tube was much enlarged near the middle, ruptured, and bleeding. The right tube had three soft swellings. Both tubes were removed. The patient died five days after operation. Post mortem was refused.

Pathologic Examination.—The left tube measured 11 cm. in length. The distal 3½ cm. was slightly swollen, 10 to 12 mm. in diameter, pink and soft. The fimbriae were blue red, slightly swollen and freely separate. The ostium was open, and the lumen patent in the smaller distal portion. The remainder of the tube was made up

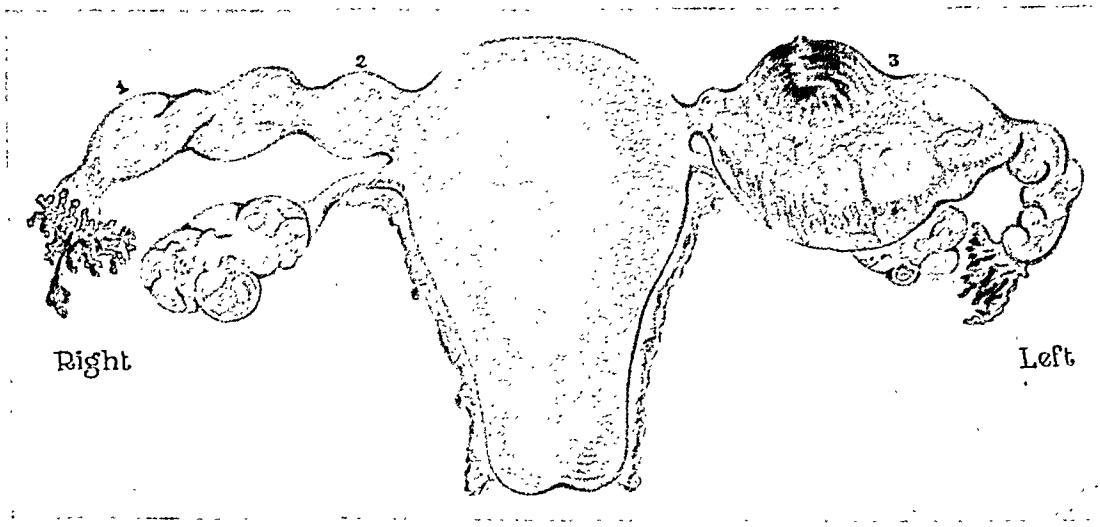


Fig. 1.—Multiple tubal pregnancies, showing sites at *1*, *2*, and *3*.

of a fusiform swelling 5 cm. in its greatest diameter, and blue red in color. A slightly raised darker red area 3 cm. in diameter had a ragged tear across it. On opening the tube, the dilated portion was filled with dark red solid blood clot. No remnants of sac nor embryo could be found, and placental strands were difficult to verify because of the extensive, rather dry clot.

The right tube was 9 cm. in length, pink red, soft and swollen throughout. The fimbriae resembled those of the left tube. A small blood clot dilated the distal end slightly, with strands of clot extending through the ostium. A sacculated swelling occupied approximately each third of the tubal length. Each saccule was 2 cm. in largest diameter, and on opening was filled with dark red soft blood clot.

Microscopic sections of the tubes demonstrated chorionic villi attached to the walls and free in the blood clot of the lumen at the three sites numbered in the drawing. The villi were of similar developmental stage. No remnants of the embryos proper were found.

SUMMARY

Attention is called to some points of difficulty in verifying reported cases of multiple simultaneous tubal pregnancy. The few requirements for acceptance of cases

are stated. The source material of 76 verifiable cases is given. A third case is presented of simultaneous twin pregnancy in one tube and a single pregnancy in the other tube.

Acknowledgment is made here to Dr. J. V. Fowler who kindly permitted use of the clinical material of this case.

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MANAGEMENT OF AN INSTITUTIONAL OUTBREAK OF INFECTIOUS DIARRHEA OF THE NEWBORN INFANT*

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INFECTIOUS diarrhea of the newborn infant, of undiscovered etiology, often carrying a high mortality rate and occurring usually as a localized outbreak among a hospital's newborn population, has recently attracted considerable attention.[1] The outbreak here reported follows closely the recorded descriptions of this condition, with the exceptions that no deaths occurred, and that the outbreak was controlled in the hospital without the interruption of the maternity and newborn nursery services. Best[2] has advocated closure of these services for the duration of the epidemic.

The newborn nursery of the University Hospital is equipped to accommodate 48 infants, with separate but adjoining rooms for premature and full-term infants, and a common nursing and professional personnel. An additional room is provided for isolation of infectious cases.

The outbreak began Sept. 8, 1937, in the nursery for prematures, with repeated vomiting and passage of loose stools by a single infant. The nature of the illness was not immediately recognized and infec-

*Read at a meeting of the Philadelphia Obstetrical Society, October 6, 1938.

tious precautions not at once established. By September 10, extreme dehydration was apparent, 6 large liquid stools having been passed in the previous twenty-four hours. On this date, the 5 other infants in this nursery began to be affected, with passage of frequent loose or watery stools. Isolation of the entire premature nursery was then established, but during the following several days new cases began to appear in the adjacent full-term nursery, eventually affecting 14 of the 28 occupants of the two nurseries. All 6 of the premature group and 8 of the 22 full-term infants were involved. Distinction between breast- and bottle-fed infants was difficult to make, as all were receiving as supplementary feeding a 5 per cent glucose solution. Ten of the sick infants, however, were classed as "artificially fed," and 4 as "breast-fed."

CLINICAL DESCRIPTION

The clinical picture resembled in all respects that described in previously reported outbreaks, except that it was in general less severe. The most constant and notable feature was the passage of frequent loose or watery stools which contained no blood, pus, or mucus, the daily frequency varying from 3 to 8. Weight loss varied from 3 to 13 per cent. Dehydration, rapid in onset and of severe degree, was the outstanding symptom in 8 cases; 2 others were mildly dehydrated. In 3 cases clinical acidosis was evidenced by Kussmaul respirations. Elevation of temperature was in no case marked or prolonged but 4 babies had a low grade fever, in one case associated with an intercurrent upper respiratory tract infection, and in another, following a blood transfusion. Vomiting was limited to 4 cases, and was not a prominent feature in any case; it usually occurred at the onset of the illness. Laboratory studies revealed leucocyte counts of from 11,000 to 14,500 per c. mm.; hemoglobin values varied from 12.5 gm. to 17.8 gm. per 100 c.c.

BACTERIOLOGY

Bacteriologic studies included stool cultures of sick and well infants, throat cultures of infants and mothers, urine cultures of mothers, and throat cultures of the nursing and professional staff as well as a survey of the formula preparation technique.

Stool cultures were plated on blood agar, Endo's medium and bromthymol blue-lactose agar, or eosin methylene blue-lactose agar. On these media cultures were uniformly negative for members of the typhoid, Salmonella and dysentery groups. The predominating organism from the stools of 20 sick and well infants was a late lactose-fermenting colon bacillus. Though Fothergill[3] and associates attribute considerable significance to the finding of such organisms in outbreaks of infantile diarrhea, its presence in this series was considerably discounted because of its recovery from well infants who did not develop diarrhea.

Throat cultures of sick and well infants showed no predominating or uniformly present organism. *B. coli* was recovered from 4 infants, hemolytic streptococcus from 2 cases. Throat culture from mothers on the ward showed only the usual flora except for 2 of the mothers who delivered after the outbreak had begun. In both these cases, hemolytic streptococci were recovered.

Urine cultures from the mothers of sick infants showed a variety of organisms, most commonly *B. coli*. From the urine of one patient's mother who delivered well after the outbreak of the disease, an organism was recovered with the biologic characteristics of members of the Salmonella group. It was partially agglutinated by paratyphoid A antiserum. This organism was not recovered from any other source and was not agglutinated by any of the sera of 12 convalescent infants, taken at periods of ten to twenty days after onset of illness. Serum agglutination studies were also carried out against staphylococcus and *Shigella paradysenteriae*, Flexner, Hiss, and Sonne. In no case was any agglutination observed.

Bacteriologic investigation of the formula preparation technique included culture of the formula, nurse's hands, throat and mask, and culture of sterilized utensils and receptacles as well as the unheated ingredients of the formula. The only suggestive finding in this study was the recovery of *B. coli* from 1 of 8 "sterile" empty formula bottles. Throat cultures from members of the professional staff showed no significant flora.

MANAGEMENT

Because of the apparent relative mildness of the disease from the outset, it was decided that, rather than temporarily closing the maternity service, the attempt would be made to control the outbreak by rigidly isolating all cases and contacts. In order to avoid the mingling of newborn susceptibles with "exposed" infants, three nurseries were established; in one, sick infants were lodged; in a second, well contacts were placed; in the third room, previously not used for that purpose, an emergency nursery for newborn noncontacts was established. The distribution of the Maternity Service at the University Hospital on 3 floors enabled us to obviate completely the possibility of chance contacts. The ill children were housed on the fourth floor, in a room adjacent to the "septic" maternity cases. "Contact" infants were held in the hospital only for the necessary maternal post-partum period, and then discharged to their homes, where follow-up visits were made by a social service worker to discover any newly developing cases. None developed, however. Cases in the "sick" nursery were discharged when diarrhea had ceased and they were able to tolerate ordinary milk mixtures.

The nursing service in each of these nurseries was completely separated from the other two, the only common service being the formula preparation. Strict aseptic precautions by the nursing staff between well but "exposed" infants was found impracticable, but cribs were separated as well as possible and nurses instructed to wash their hands thoroughly after changing or feeding each infant. As soon as the regular ("contact") nursery was emptied by discharge or transfer, it was thoroughly scrubbed and aired, and the unexposed newborn infants transferred to it from the "emergency" nursery.

THERAPY

The sick infants were given 1:10 powdered protein milk, followed by skimmed lactic milk and 2 per cent milk as tolerated. Dehydration was combated by the subcutaneous injection of lactate-Ringer's solution; acidosis was controlled by intravenous and subcutaneous sodium lactate. Transfusion of citrated blood was employed for 3 premature infants with general debility and extreme dehydration.

All of the sick infants recovered. On follow-up one proved to have continued to pass loose stools for a week after discharge. Another who did not return for follow-up, continued to have loose stools for three months. The others remained symptom-free. It is interesting to note that none of the "contacts" developed diarrhea after discharge. None of the infants born after establishment of the emergency nursery became ill.

COMMENT

In most essential aspects, the outbreak here reported resembles those previously described as "infectious diarrhea of the newborn," the outstanding features being frequent, watery stools, rapid dehydration, afebrile course, high morbidity, and inability to demonstrate an etiologic agent, in spite of intensive bacteriologic study. The absence of mortality is, however, in contrast with the usual high percentage of deaths reported, although it is not unique.[1]

SUMMARY

An outbreak of infectious diarrhea of undiscovered etiology, affecting 14 of 28 infants in a hospital nursery for the newborn, is reported.

No deaths occurred. A method of management is described, by which the addition of new susceptibles to the infected group is avoided, without interruption of the maternity service.

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DISCUSSION

DR. THEODORE S. WILDER.—It is perhaps appropriate here to mention two small epidemics among the newborn babies at the Germantown Hospital, which appear to resemble in all respects the epidemic Dr. Roddy has described.

The first occurred in September, 1937, affecting 5 premature infants only, and was characterized by sudden onset with vomiting, and by 12 to 15 watery, yellow or green stools daily, which were free from blood or mucus. Dehydration was extreme, and was accompanied by cyanosis, which disappeared on administration of subcutaneous fluids. These infants all recovered within three weeks, thanks largely to the use of glucose and salt or lactate solutions under the skin, thrice daily.

A year later, almost to the day, a second outbreak occurred, clinically identical with the first. This involved 11 infants; treatment was the same, and there were three deaths. But of the deaths one was a premature infant, and the other two were babies who, discharged at fourteen days, apparently well, promptly developed enteritis at home, and were readmitted to the ward several days later, in a moribund condition.

Bacteriologic search for a causative organism revealed a motile, nonlactose fermenting, gram-negative bacillus in all 9 of the infants whose stools were cultured. This organism was agglutinated by the serum of one of the patients a month later in 1:200 dilution, and is being studied further.

A feature of both outbreaks at the Germantown Hospital was the fact that all the cases occurred within a few days of each other, as though there had been a sudden exposure, following which there were no secondary cases. Whether cessation of the epidemic was due to precautions taken, or to the fact that the infectious source no longer was operative one cannot say. The results, however, justified our not closing the maternity service, as has been advocated in connection with similar, but perhaps more severe, epidemics in New York Hospitals.

DR. OWEN J. TOLAND.—I have recently read an article from New York which states that once a diagnosis of epidemic diarrhea has been established in a maternity nursery, the only thing to do is to discontinue completely the maternity service. I have also seen recently an article which, in view of spreading epidemics, advised that the only thing to do was to re-educate the public to have their babies at home.

Bertolotto, U.: Short Wave Therapy to the Hypophysis in Certain Forms of Metrorrhagia, Folia Gynaecologica 25: 377, 1938.

The author reports upon a new method of therapy for various forms of metrorrhagia by the use of short wave treatment applied to the hypophysis. He discusses the genesis of certain types of bleeding, outlines his method of experimentation, form of application and technic. Based on his experimental research he explains the mode of action of short waves and enumerates the advantages which this method of treatment presents in various forms of bleeding, both in gynecology and obstetrics.

MARIO A. CASTALLO.

AN UNUSUAL CASE OF CHRONIC INVERSION OF THE UTERUS*

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CHRONIC inversion of the uterus per se is sufficiently rare to make it worth while reporting every case and what makes my case still more unusual is the fact that the inversion involved not only the body of the uterus but also the cervix including the portio vaginalis (Fig. 1). In a rather superficial examination of the literature I have been unable to find a report of a similar case.

CASE REPORT

M. S., white, housewife, aged 24 years, married 5 years, was born in New York. No operations. Menstruation began at 12, every thirty-five days, periods lasting two days, scant in amount and without pain. Sexual life apparently normal. Took contraceptive precautions for four years.

Her last period was on June 30, 1935. Expected date of confinement April 7, 1936. She had a normal pregnancy.

Patient began to have irregular pains on April 8, 1936. On April 9 she was admitted to a private hospital. After twelve hours the patient was sent home. She continued to have irregular pains for ten days. At about 11 P.M. on April 19 the bag of waters ruptured, and the patient was apparently about to deliver. She was rushed to the hospital, and the baby was born spontaneously. The placenta was delivered with difficulty, i.e. there was considerable pressure necessary to deliver it. This took place about twenty minutes after the birth of the baby.

The delivery was followed by a severe post-partum hemorrhage which the family physician was unable to control. The patient repeatedly bled through the packing in the vagina. One of my associates who was called in consultation told me that he thought the patient had a cervical tear but that she bled so furiously and was in such bad shape that he could not attempt a repair. She was packed and repacked. She received a transfusion at 1:50 A.M. and another at 3:30. The bleeding was finally controlled the following day. The anemia and shock were treated by transfusions, infusions, liver, iron, etc.

During her post-partum period the patient complained of severe backache and inability to move her legs. She had a peroneal paralysis of both legs with foot drop. She remained at the hospital for a fortnight and was taken home in an ambulance. At home she was bedridden because of the paralysis and there was continuous vaginal spotting.

On June 5, 1936, she had a sudden severe vaginal hemorrhage and was brought to the Morrisania Hospital much exsanguinated. The condition was readily diagnosed. There was a firm bleeding mass the size and shape of an inverted pear filling the vagina, and a bimanual examination revealed the absence of a uterus above the vaginal vault.

The vagina was packed and the patient was given a transfusion. The packing had to be replaced several times because of saturation. On June 8 an attempt at a careful examination for the purpose of deciding the best method of treatment was accompanied by such severe hemorrhage that it had to be abandoned. However, we obtained sufficient information to make us feel that a vaginal operation was indicated as soon as the patient's condition permitted. In the meantime the patient's condition continued to be rather serious. Her pulse was rapid and weak and she continued to bleed through the packing. On the night of June 9 she began to bleed profusely and her general condition grew rapidly worse. However, we felt that

*Presented at a meeting of the New York Obstetrical Society, November 8, 1938.

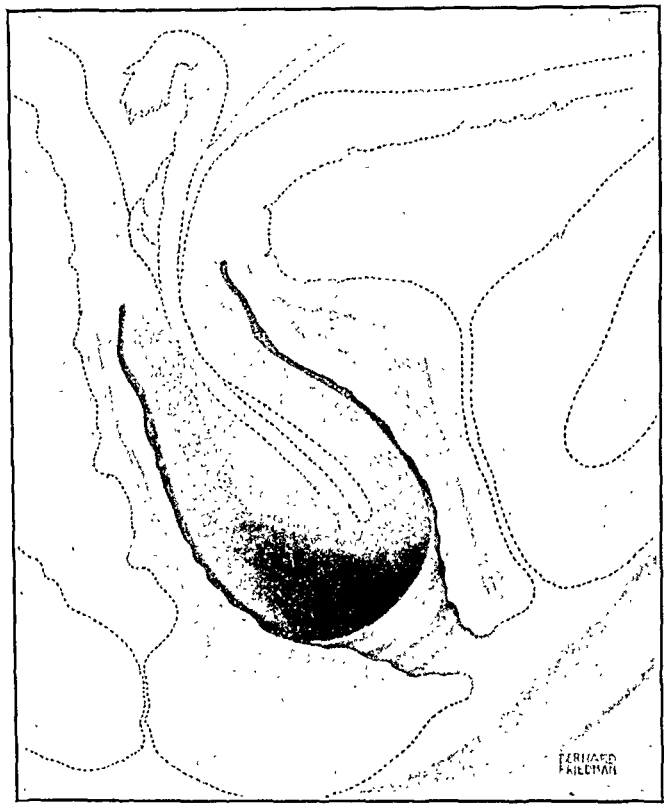


Fig. 1.—Complete uterine inversion including vaginal portion of cervix.

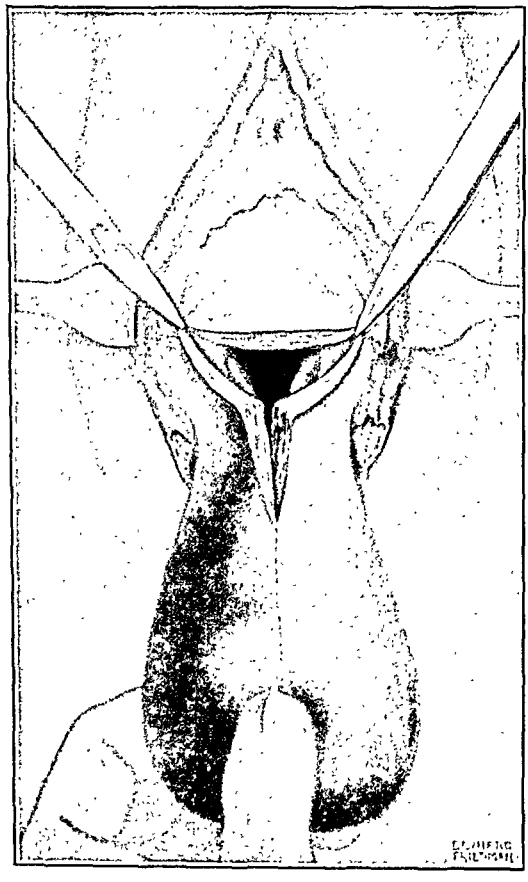


Fig. 2.—Showing transverse incision above edge of cervix, bladder pushed up, and peritoneal cavity opened.

under the circumstances a hysterectomy would be fatal and suggested an exposure of the inverted uterus, controlling the bleeding points with the coagulation cautery to be followed by another transfusion.

The patient reacted so favorably to the above treatment that on June 13 she was prepared for a vaginal replacement according to the Spinelli method.

At the operation, when the vagina was retracted and the inverted uterus exposed, I was greatly surprised to find that there was no cervical cuff. Apparently the inversion had proceeded and involved the entire cervix, including the portio vaginalis. At the base of the inversion the mucous membrane of the uterus was continuous with the mucous membrane of the vagina without a ridge or scar. This necessitated a slight change in the technique of the operation.

The tip of the inverted cervix was identified by palpation and a transverse incision was made in the mucous membrane of the vagina just above it. With a sound in the bladder, the bladder wall was exposed and separated from the anterior wall of the cervix and vagina. The vesicouterine fold of peritoneum was opened, exposing the edge of the cervix and the inversion funnell (Fig. 2). An incision was made from the cervix to a little beyond the apex of the fundus and the uterus turned "inside-in" without difficulty. Here another unexpected situation awaited us. In our efforts to control the bleeding we had coagulated the greater portion of the anterior wall of the uterus. The tissues were gray and bloodless. We were extremely reluctant to sacrifice the uterus in such a young woman and so we excised the dead parts of the anterior wall of the uterus and brought the healthy raw edges together by layers of chromic catgut. Tubes and ovaries were found normal. A rubber tube drain was placed in the cul-de-sac through a stab wound and another into the vesicouterine space. Peritoneum, fascia, and mucous membrane were sutured with chromic catgut.

The perineum which had been lacerated during the delivery and subsequent manipulations was repaired. The patient made an uneventful recovery.

During her convalescence the neurologic and orthopedic departments of our hospital helped us take care of the paralysis, and on July 5 exactly a month after her admission the patient walked out of the hospital a well woman.

For about a year the patient did not menstruate but had no signs of menopause. Just as we were about to make a hormonal study of the blood and urine, the patient had a normal menstruation. She has menstruated regularly since. A follow-up note by my resident on Dec. 17, 1937, reads as follows: "Menses regular, no leucorrhea, excellent anatomic result."

DISCUSSION

DR. ONSLOW A. GORDON.—In 1934 I reported a series of 7 cases of inversion of the uterus, all operated upon without mortality. One patient in the series, who had a Spinelli operation, died two years later following rupture of the uterus, occurring before the onset of labor. One must bear in mind that when the Spinelli operation is done, subsequent pregnancies are a dangerous complication.

I believe that the abdominal operation devised by James Huntington, of Boston, would have been particularly apropos in Dr. Aranow's case, for there was no apparent cervical constriction. It is the cervical constriction in chronic inversion which is the difficult factor in reduction of the inversion. Masson, however, reported a series of patients with chronic inversion operated upon abdominally in which there was marked cervical constriction. He incised the cervix in the midline, posteriorly, and, thus, easily reduced the inverted corpus abdominally.

The advantages of the abdominal operation are: The exposure is much better. There is usually much less bleeding. There is less trauma to the body of the uterus. The woman is left in a much safer condition for subsequent pregnancy. Should hysterectomy be necessary it may be more readily done either before or after reduction of the inversion.

DR. DAVID NYE BARROWS.—About six years ago I reported before this Society a similar case of complete inversion operated upon abdominally. The procedure was extremely simple as the cervix had risen nearly to the pelvic brim and an incision through the posterior lip into the vaginal vault made it easy to split the

posterior uterine wall, and reinvert the uterus. That patient was advised not to become pregnant for five years, but after four years she conceived. An elective cesarean section was done, and the old scar found to have healed perfectly.

DR. EDWIN W. HOLLADAY.—Having noticed the technical difficulties in two Spinelli operations and the simplicity of the abdominal operation, I wish to corroborate what Dr. Barrows has said as to the superiority of the abdominal approach. I believe Dr. Aranow would have found this so in his case.

The technique is very simple. With the operator working through the abdominal wound, he can dilate the constricting ring or cut it posteriorly. A third assistant, with a hand in the vagina, pushes up the inverted uterus to the vault of the vagina. The operator can now seize in the hollow of his hand the still inverted uterus. By kneading with the tips of his fingers and with gentle traction, he will be amazed to see the uterus practically correct its position itself.

DR. F. A. WURZBACH, JR.—To stop the bleeding in this case I had to cauterize the anterior surface of the uterus. In cases that do not have the rough treatment to which I had to subject this uterus I do not doubt that the abdominal operation would be better. This patient, however, was in pretty bad condition and undoubtedly the peritoneal cavity would have become infected.

DR. EDWARD G. WATERS.—I think it may be worth while to comment on the advisability of doing a vaginal examination on bleeding patients post partum and before discharge from the hospital. There are three things that cause a woman to bleed immediately post partum: cervical lacerations, rupture of the uterus, and inversion of the uterus. There is no way of telling which of the latter two may be present except by an adequate vaginal examination in the presence of bleeding that is demonstrated as not coming from the cervix.

We have seen five cases at Margaret Hague Maternity, and one fatality occurred where the inversion was not recognized. The other four were immediately replaced and then shock treatment was instituted. The response of the patients was so good that one or two days later you would not know that anything serious had happened.

DR. ELIOT BISHOP.—Cases of inversion of the uterus must be placed in two categories: One as to time—is it acute or chronic? the other as to the physical state—is the patient infected or in shock?

If the case is in the first category, and inversion has just occurred, immediate laparotomy, with presumably a transfusion, and traction from above according to the method published by Huntington, Irving and Kellogg some years ago, ought to bring cures with a low mortality and morbidity. If the case is in the first category, but not infected or shocked, an elective Spinelli operation should be the choice, for, thus, the inversion can be reduced with no loss of organs.

If the case is in the second category and is infected, but not in shock or with hemorrhage, she must be treated for infection, in any way that seems best suited. If shock and hemorrhage exist, treatment should be directed toward them; transfusion should be given, and it would seem to me that the suggestion of the reader of the paper, local cauterization, deep suturing and firm packing, are the first methods of attack.

DR. ARANOW (closing).—We are allowed to do vaginal work only on our service at the Morrisania Hospital. As a result I have learned to prefer vaginal work. I find the vaginal route just as easy and a little safer. In this particular case the abdominal route was considered but because of the marked edema of the endometrium, a simple reduction of the inversion without extensive incision of the corpus uteri seemed impossible.

dimensions of the bony structures of the pelvis and fetus, therefore, has certain limitations, and to draw definite conclusions as to the outcome of labor without considering the whole picture is not only hazardous but unscientific. In other words, the greatly useful knowledge which these roentgen methods have given us must be properly assimilated with our greatest therapeutic weapon, namely, clinical experience.'' I would add that not only the roentgenologist but, since he is responsible for the patient's welfare, the obstetrician should be able to interpret intelligently roentgenograms made for pelvic mensuration.

INCIDENCE OF OPERATIVE INTERVENTION IN THE SERIES

In this series of primiparous patients operative intervention was used in 113 instances. The incidence of operative intervention in relation to pelvic type was as follows:

Dolichopellic type,	15 instances	or 16.3	per cent
Mesatipellic type,	49 instances	or 18.0	per cent
Brachypellic type,	41 instances	or 19.5	per cent
Platypellic type,	8 instances	or 30.7	per cent

The operations are divided as follows:

Cesarean section,	15 instances
Version and extraction,	4 instances
Midforceps,	18 instances
Outlet forceps,	76 instances

The incidence of outlet forceps 76 times in 600 labors should be commented upon inasmuch as many of these patients might have delivered spontaneously if spontaneous birth were an object in itself. It is our belief, however, that in many instances in the primiparous patient when the second stage has been prolonged and the head rests on the perineum, delivery by forceps is often an advisable procedure. The term ''forceps control'' for these cases is a descriptive term and perhaps should be employed.

INCIDENCE OF CESAREAN SECTION ACCORDING TO PELVIC TYPE

Cesarean sections, 15 in number, occurred as follows:

Dolichopellic type	0 instances	or 0	per cent incidence
Mesatipellic type,	2 instances	or 0.7	per cent incidence
Brachypellic type,	9 instances	or 4.3	per cent incidence
Platypellic type,	4 instances	or 15.4	per cent incidence

A brief analysis of these 15 cesarean sections should be of interest and is as follows:

CASE 1.—No. 41108. Small brachypellic type pelvis, 9.5-11.25 cm. Trial of labor followed by cervical cesarean section. Child, 3,050 gm. Lateral roentgenogram during labor showed no attempt at engagement of fetal head.

CASE 2.—No. 64003. Platypellic type pelvis with double promontory, 10.25-13.25 cm. No engagement at term, patient 36 yr. of age. Elective classical cesarean section. Child 3,275 gm.

CASE 3.—No. 21769. Small brachypellic type pelvis, 8.5-11 cm. Rachitic changes in sacrum. Elective classical operation. Child 2,600 gm.

CASE 4.—No. A 36533. Brachypellic type pelvis, 10.25-11.5 cm. Cervical cesarean section after trial of labor. Child 2,995 gm.

in the cure of a fistula which was operated on 5 times unsuccessfully. He prepared his "cuff," as in his well known tracheloplasty, except that he slit on both sides for greater mobility, had no trouble in thus separating the anterior vaginal wall from the bladder, repaired the defect in the latter and brought the "cuff" down and inverted it into the coned out cervix. He thus obtained the advantage of bringing an intact vaginal wall over the sutured bladder, but his method is only possible where the fistula is very low for obvious reasons.

It occurred to me that the utilization of the cystopexy with an intact vaginal wall over it would insure a perfect healing; the following case, with technique used therein, is therefore reported.

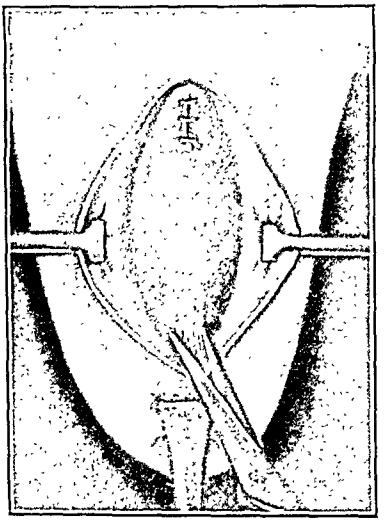


Fig. 3.

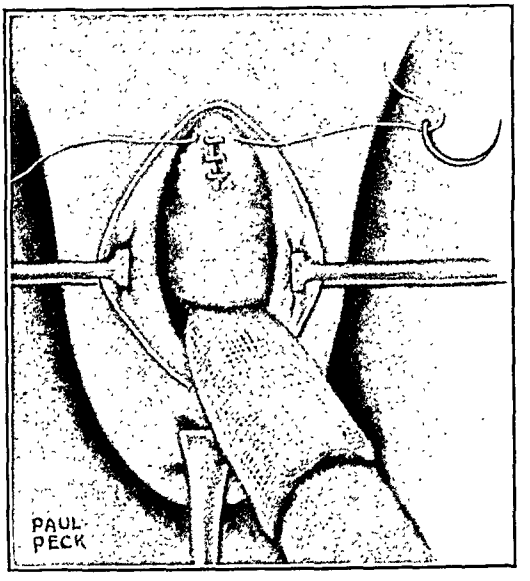


Fig. 4.

Fig. 3.—Vaginal flaps retracted to sides, vaginal mucosa above fistula separated from bladder as in Fig. 2, and uterovesical ligament severed.

Fig. 4.—Suture of chromic No. 2 inserted in bladder above fistula and blunt dissection of bladder begun.

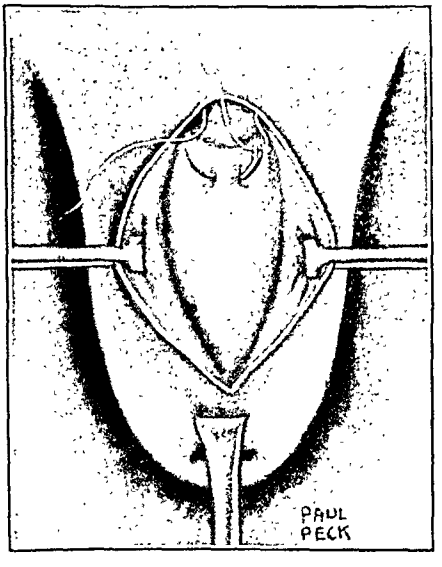


Fig. 5.

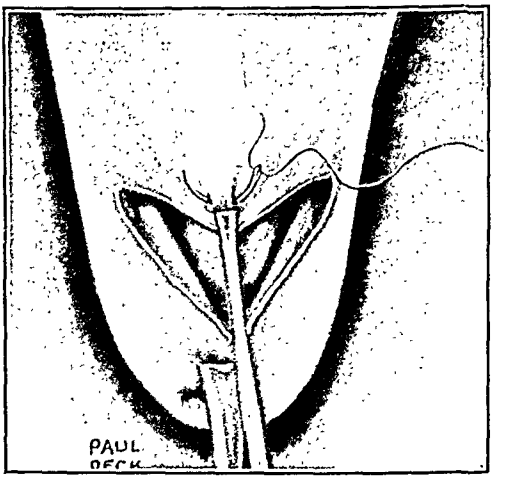


Fig. 6.

Fig. 5.—Upper suture taking bite in uterus somewhat above internal os which will revolve bladder transversely.

Fig. 6.—Upper part of freed vaginal mucosa brought down and sutured below attachment of bladder.

A MODIFIED STURMDORF OPERATION FOR VESICOVAGINAL FISTULA*

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WITH better training in the use of the prophylactic forceps and episiotomy, and the practical elimination of the midwife, vesicovaginal fistula due to poor obstetrics has almost disappeared.

A great number of the fistulas seen today are due to radium used in the treatment of carcinoma of the uterus. Improved technique and the greater use of the x-ray are diminishing that as a source. An occasional case, however, is still seen and the problems of its repair still exist.

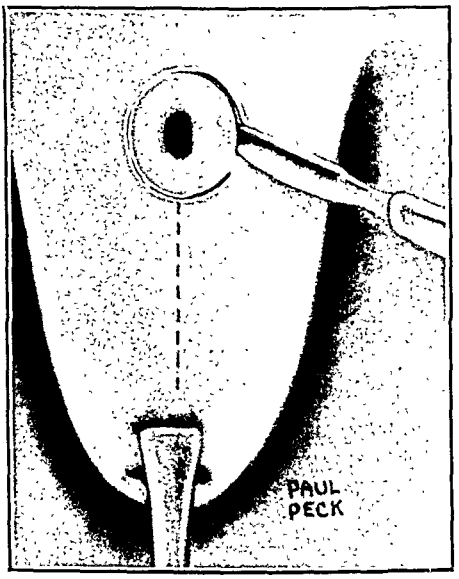


Fig. 1.

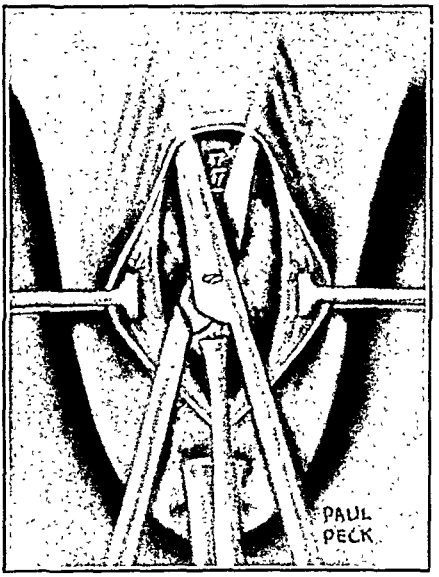


Fig. 2.

Fig. 1.—Incision of vaginal mucosa around fistula about one-fourth of an inch from edge which is freed and then used to close fistula. Incision in midline below this to reflect flaps to side shown by dotted line.

Fig. 2.—Flaps reflected to side and blunt scissors dissecting vaginal mucosa from bladder above fistula.

From the time of Marion Sims there have been innumerable modifications of the operation for the cure of fistula and one hesitates to add anything to the voluminous literature on the subject.

In addition to the three cardinal postulates of Sims, that is, proper exposure; a reliable suture and an empty bladder; it seems that a fourth, though mentioned by different writers, might be emphasized, namely, the suturing of the bladder and vaginal walls in different planes.

In the technique described below two ideas were utilized which seem to insure success in the great majority of vesicovaginal fistulas situated in the upper two-thirds of the anterior vaginal wall. In 1919 George Gray Ward described his operation for cystocele and coined the word "cystopexy" for part of his technique. He did this by freeing the bladder from its cervical attachment, reflecting it upward by blunt dissection, revolving it on its transverse axis, and suturing it to the uterus somewhat above the internal os. In 1925 Sturmdorf described the use of his "cuff"

*Read at a meeting of the Brooklyn Gynecological Society, October 7, 1938.

IMPLANTATION OF OVARY IN THE UTERINE CORNU*

MARGARET CASTEX STURGIS, M.D., F.A.C.S., PHILADELPHIA, PA.
(From the Department of Gynecology of the Woman's Medical College of Pennsylvania)

WHILE the implantation of an ovary or part of an ovary in the uterine cornu is not new, it still is not a common surgical procedure. The results in this particular case justify the plea for more conservative ovarian surgery in young women suffering with complicated chronic pelvic inflammatory disease in which the whole of both tubes and one ovary or even one ovary and part of the other must be removed.

This patient, a colored woman twenty-seven years of age, married eleven years, was first seen in December, 1931. She was admitted to the Clinic of the Hospital of the Woman's Medical College, seeking relief from constant backache, pelvic pain, and discomfort. She gave a history of three abortions early in her married life, reported as spontaneous and of about three months' duration. Five months previous to admission she had had an attack of pelvic inflammation, and at the time of admission to the hospital, pelvic examination revealed an adherent retroverted uterus with bilateral tender adnexal masses. Sedimentation rate was sixty minutes and Wassermann was negative.

The patient was operated upon Jan. 2, 1932. Bilateral pyosalpinx with inflammatory adhesions, oophoritis, and adherent retroverted uterus were found. It was necessary to remove both tubes and all of the right and part of the left ovary. The left ovary was resected, preserving intact the utero-ovarian ligament with its small blood vessel and nerve supply, and was implanted in the left cornu after a wedge-shaped removal of the cornu had been made. The cut surface of the ovarian cortex was implanted on the uterus over the tubal opening and the intra-abdominal surface was peritonized. The round ligaments were plicated and sutured to the post surface of the uterus after the Estes method, covering both uterine horns. This shortening of the round ligaments likewise secured the anterior position of the uterine body. The uterus was normal in size and without demonstrable pathology. The patient made an uneventful recovery and continued the menstrual function as usual. In September, 1932, Dr. Virginia Alexander, her private physician, reported that the patient was pregnant. Unfortunately, however, the patient aborted a three and one-half months' fetus on Oct. 16, 1932.

The patient was not seen again until February, 1938, when she gave a history of having been perfectly well until October, 1937, when she again began to suffer with lower abdominal pains and backache. The periods prior to this time had been regular, twenty-eight-day interval and five days' duration, amount moderate. October, November, and December periods had a longer interval, were irregular, duration more prolonged and flow scanty. The last menstrual period was Dec. 29, 1937. There was no January period so the increasing backache and pelvic discomfort brought the patient to the hospital.

Examination revealed a firm, irregular enlargement of the uterus. A diagnosis was made of multinodular uterine myoma. A pregnancy test was negative so the patient was operated upon Feb. 10, 1938. A multinodular myoma involving the entire uterine body was found with the small amount of ovarian tissue at the left cornu to which were omental adhesions. There were no other adhesions in the pelvis. The omentum was ligated and the attachment to the ovary incised and a supravaginal hysterectomy was done. The patient made an uneventful recovery.

This case is important in that pregnancy did occur; hence there was restoration of the "opportunity" for pregnancy.

*Read at a meeting of the Obstetrical Society of Philadelphia, October 6, 1938.

Mrs. H. B., 27 years of age, married four years, was admitted to Beth-El Hospital, Apr. 27, 1934. Previous history irrelevant. She was delivered in January, 1934, after a prolonged labor, with midforceps, of a living child which died four weeks later of congenital heart disease. Patient began to dribble urine the day after delivery and continued until present admission. Condition on admission was excellent except for complete loss of urine from a vesicovaginal fistula situated about midway between urethra and external os, measuring about 2 cm. in length and somewhat less than a centimeter in width. Except for the scars around the fistula, the parts were in good condition and practically ready for repair.

The technique used was as follows (Figs. 1 to 7): An incision in the vaginal mucosa around the fistula about a fourth of an inch from its edge was made, and the flap freed, and used to help close the fistula. An incision in the vaginal wall in the midline below this was made and the two flaps freed laterally for some distance, then upward around fistulous opening and above it for about an inch and a quarter, freeing the vaginal wall from the bladder by blunt dissection while

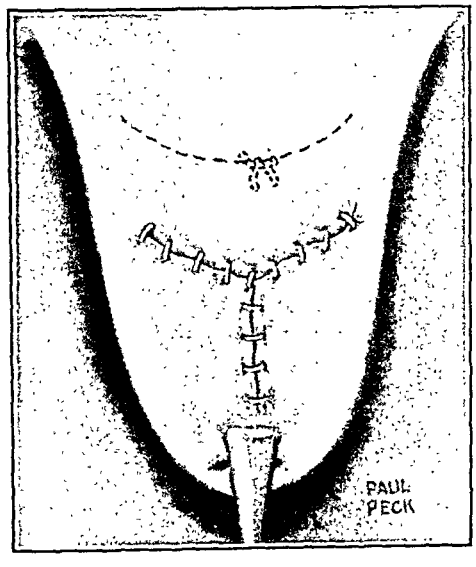


Fig. 7.—Operation completed, showing vaginal closure some distance below bladder attachment.

the latter was held taut by an Allis clamp. The vesicocervical ligament was then severed and the bladder bluntly dissected upward to beyond the internal os. A cystopexy was then done as described by Ward, taking a bite in the bladder at the upper edge of repaired fistula and suturing it to body of the uterus above the internal os. The upper edge of vaginal mucosa was then brought down and sutured to the uterus below the new attachment of the bladder, thus giving the fistula a wall of uterus posteriorly, in addition to its own closure and an intact vaginal mucosa over it. The original lower flaps were then sutured partly transversely to take up the slack by having brought the upper flap down. An indwelling catheter was left in the bladder for seven days. The bladder was washed twice daily with 1 per cent phosphoric acid to prevent encrustations.

I do not offer this technique as a method for every kind of fistula. Many defects are so situated that different methods of approach will be necessary, but the principle of closing the bladder and vaginal openings in different planes will add much to the success of any operation for fistula.

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A preoperative diagnosis of intra-abdominal hemorrhage from unknown origin associated with a fibroid uterus was made. The patient was given a preliminary transfusion of 500 c.c. of whole blood and then a laparotomy was done. The peritoneal cavity contained at least one quart of free blood and clots. The uterus was slightly enlarged, firm in consistency, anterior and mobile. Arising from the posterior fundal region was a large sessile fibroid measuring 7 by 5 inches whose lateral aspect presented many dilated varicose veins. One of the larger varicosities had ruptured and at this site was covered with a clot. When this was dislodged active bleeding ensued. A supracervical hysterectomy was performed. The postoperative course was uneventful and the patient was discharged on the fifteenth day in good condition.

The second case presented a similar clinical picture, and profiting by the previous case, the condition was considered preoperatively.

N. H., aged 31, colored, married, was admitted to Kings County Hospital, Service of Dr. Charles Gordon, on Aug. 3, 1937, at 1:10 P.M. in a state of collapse. The history obtained was of no help except to elicit that there had been no pregnancies and that her menses had been regular. The last period occurred in July.

The patient was well until eleven o'clock the morning of admission when she experienced a sudden, persistent, sharp pain in the right lower quadrant of the abdomen. This weakened her considerably, hence she sought hospitalization and was admitted via ambulance.

On admission the blood pressure was 56 systolic and zero diastolic, temperature 99.2°, pulse 88, feeble and inconstant, respirations 26. The patient was restless and apprehensive, skin cold and clammy. The abdomen was soft and tender over the right lower quadrant where a firm mass the size of a large orange could be felt. Vaginal examination revealed the cervix tender to motion and a mass in the left fornix which was firm in consistency, the size of a hen's egg. The abdominal mass could not be felt through the vagina.

White blood cells 9,000, with 69 per cent polymorph leucocytes and 31 lymphocytes; red blood cells 3,900,000, with 78 per cent hemoglobin (Sahli). The urine was negative. A preoperative diagnosis of intra-abdominal hemorrhage due to either a ruptured tubal pregnancy or "rupture of a vessel on a fibroid" was made. The patient was treated for shock and when she reacted a laparotomy was done. At operation the peritoneal cavity contained between two and three quarts of blood. The uterus was the seat of multiple fibroids, of which two were pedunculated and attached to the fundus. The larger one, measuring 10 cm. in diameter, had undergone complete torsion resulting in a ruptured varix on the posterior surface. A fundectomy including both fibroids was done. The patient received 200 c.c. of blood by autotransfusion and an additional 700 postoperatively. Her stay in the hospital was uneventful and she was discharged on the thirteenth day in good condition.

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The second important result and that of prime importance was the maintenance of a normal menses for six years. The atrophy of the ovary as recognized on microscopic section and evidenced clinically by dysfunction during the last three months, could be explained as being hastened by the interference in the blood supply by the fibroid growth in the uterus.

This case does not present the objections to this operation sometimes advanced. There had been no pain experienced at the ovarian site. The ovary had not become cystic and the atrophy had not commenced early.

The operation for the removal of the myomatous uterus permitted the study of the anatomic and histologic end results following an ovarian transplant into the uterine cornu.

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1930 CHESTNUT STREET

MASSIVE INTRAPERITONEAL HEMORRHAGE RESULTING FROM RUPTURE OF A SUPERFICIAL VEIN OF A UTERINE FIBROMYOMA*

ANTHONY L. SHELFO, M.D., BROOKLYN, N. Y.

(From Kings County Hospital, Long Island College of Medicine Division)

RUPTURE of a vessel situated on the surface of a uterine fibroid is an extremely rare condition as evidenced by the few reported cases in the literature. The vessel usually involved is a vein running between the capsule of the fibroid and the peritoneum.

Most writers in discussing complications of fibromyomas fail to mention this condition. Reference to it has been in the form of case reports.

The two cases about to be reported bring the total number in the literature to 48. They are reported because of their rarity, their gravity, and the problems they offer in differential diagnosis from such conditions as ruptured ectopic pregnancy, ruptured corpus lutein cyst with hemorrhage, or torsion of an adnexal tumor.

CASE REPORT

L. G., aged 52, colored, married, gravida xiii, para ii, was admitted to Kings County Hospital on April 19, 1936, in shock. Her last period occurred two weeks before admission to the hospital. The patient was well until eight o'clock in the morning of admission when she was seized with a sharp lower abdominal pain which caused her to collapse. The pain persisted and her condition grew rapidly worse.

On admission she had a blood pressure of 50 systolic and zero diastolic, pulse 84 and feeble, temperature 100.8° F. The skin was cold and clammy. Abdominal examination revealed a tender, firm, ballotable mass in the lower mid-abdomen the size of a large grapefruit. Vaginal examination showed the mucous membrane to be pale in color. The cervix was tender to motion and continuous with it was the mass felt in the abdomen.

White blood cells 9,200, with 62 per cent polymorph leucocytes and 38 per cent lymphocytes; red blood cells 4,200,000, hemoglobin (Sahli) 80 per cent. Urine showed two-plus albumin and otherwise was negative.

*Read at a meeting of The Brooklyn Gynecological Society, December 2, 1938.

She was reoperated upon May 25, 1933. A soft infiltrating tumor was found; four-fifths of which was removed from the left cerebellar hemisphere. *Diagnosis:* Medulloblastoma.

Three series of x-ray treatments were given, and the patient continued to live in fair condition, having bouts of vomiting and weakness until her death October, 1936.

The question that concerns the gynecologist is, shall pregnancy be terminated in cases complicated by brain tumor? The literature does not reveal an unanimity of opinion.

2019 PINE STREET

CERVICAL DYSTOCIA DUE TO SCARS FROM DEEP CAUTERIZATION

HARRY JAMES JORDAN, M.D., PITTSBURGH, PA.
(From the St. Francis Hospital)

PATIENT in this case had a deep cervical cauterization about nine months previous to the labor under discussion. This was not followed up by the usual dilatation of the cervix at the end of the six weeks' period. On July 17, 1938, at 10:30 P.M. I was called into consultation by the family physician at the patient's home.

Mrs. J. W., aged 33, gravida iii, para iii, all previous labors spontaneous and with no difficulty. She had been in good active labor for the past fifteen hours. Examination revealed a vertex presentation, L.O.A. position, presenting part engaged, no evidence of disproportion, fetal sounds L.L.Q., rate 120, external measurements within normal limits, membranes ruptured.

On rectal examination the presenting part was easily felt. There was no effacement and the external os would not admit the tip of the examining finger. At this time the contractions were of good quality, every three to four minutes. The family physician stated that this had been the case for the past fifteen hours. The patient was given ¼ gr. of morphine sulphate, and I remained with her until 7 A.M. the following morning. During this time the contractions remained the same and repeated rectal examinations revealed no further dilatation.

The patient was then advised to enter St. Francis Hospital at which time vaginal examination revealed a large, soft, bilaterally lacerated cervix, which would not admit the tip of the examining finger. The presenting part was fixed; could be felt in both fornices and the diagonal conjugate was ample.

One-fourth grain of morphine sulphate and 1/200 gr. of scopolamine were given on admission at 8 A.M. and at 4 P.M. of that afternoon. No change was noted in the caliber of the cervix, after a total labor of thirty-two hours.

Under gas ether anesthesia the operative area was prepared in the usual manner, following which each cervical lip was grasped with two pair of ring forceps. The anterior lip was incised as far as the bladder and the posterior lip as far as the rectum. The hand was then inserted completing the dilatation and delivery of a healthy male infant weighing 7 pounds 8 ounces by podalic version. The cervical incisions and old bilateral lacerations were approximated with No. 2 chromic catgut, after which the placenta was expressed. There was a very resistant fibrous ring at the level of the internal os which would admit two fingers and could probably be attributed to the scarification resulting from the earlier deep cauterization. Both the patient's and infant's stay in the hospital was uneventful and they were discharged on the twelfth day in good condition. The cervix was well healed and looked better than on admission.

BRAIN TUMOR COMPLICATING PREGNANCY*

BERNARD MANN, M.D., PHILADELPHIA, PA.

THE coincidence of brain tumor and pregnancy is rare. The literature reveals about 30 cases of this complication. According to Cushing, brain tumors, particularly gliomas, may either arise during pregnancy, or more likely their growth becomes accelerated during this state.

K. L., aged 24 years was admitted to the Mount Sinai Hospital on Sept. 23, 1932 because of severe headaches, dizziness, vomiting, and weakness of the left arm and left leg.

The last menstrual period was Feb. 17, 1932. The expected date of confinement was Nov. 24, 1932. During the first three months she vomited frequently, mostly in the mornings. She did not vomit during June and July, but in August the vomiting recurred.

Her past medical history was negative. She had two normal deliveries, two and four years ago, vomiting only the first two months with each.

The general physical examination on admission was as follows: The blood pressure was 114/75. The heart and lungs were normal. There was no edema. The uterus was enlarged to the size of a six months' pregnancy, fetal heart sounds were heard in the left lower quadrant.

The urine was negative except for a trace of albumin. Hb. 80 per cent; R.B.C. 4,270,000; W.B.C. 10,700; polymorphonuclears 75; small monocytes 24; large monocytes 1; total nitrogen, 26.4; urea nitrogen, 11.2; alkali reserve, CO_2, 45 volume per cent; blood sugar, 94; calcium, 9.6; chlorides, 572; Wassermann, Kolmer, and Kahn tests negative. Liver function test, bromosulphthalein, before dye injection, 0 per cent; fifteen minutes after injection 0 per cent; thirty minutes after injection, 0 per cent; sixty minutes after injection, 0 per cent. Icterus index, blood serum 3.

X-ray of skull and chest were negative. A lumbar puncture was done, the spinal fluid was under 8 mm. of mercury pressure, examination of the fluid was negative. She had a marked ataxia and slight weakness of the left arm and leg. There was a choked disc of two diopters of the left eye and one diopter, the right.

She was kept under observation and repeatedly examined to determine the location of the brain tumor.

The headaches, dizziness, and vomiting continued, becoming more severe. On October 14 she could not be aroused. It was then decided to terminate the pregnancy. A cesarean section was done under local anesthesia. She was delivered of a living female child, which died the next day. The day following the section she was not so stuporous, complained of headache but no vomiting. The next day the headache continued and the vomiting recurred, both sphenopalatine ganglia were cocainized, which gave her relief for a day, the above procedure was repeated with no relief.

The prompt improvement after evacuation of the uterus at the thirty-fifth week of pregnancy may have resulted from the decrease in blood volume and diuresis which occurred at this time.

Nov. 12, 1932, Dr. Francis C. Grant explored the posterior fossa by means of a suboccipital craniectomy and found the left cerebellar hemisphere to be larger than the right. Tap of this hemisphere revealed a deep seated tumor. Owing to the patient's condition the removal of the tumor was not attempted. She was discharged from the hospital December 7 in quite satisfactory condition, which continued until April, 1933 when the symptoms of vomiting and nausea, pain in left side of her head, cramp and pain in left arm and leg returned.

*Presented at a meeting of the Obstetrical Society of Philadelphia, December 1, 1938.

goblet cells commonly multiply on the inside of an ovarian cyst rather than on the surface, this leaking of contained fluid from a nonbenign cyst is the commonest cause of metastatic recurrences. Occasionally if the transported cells are of low vitality they may atrophy or a chronic inflammatory process may enclose the implanted tissue and inhibit its growth. Otherwise the metastasis continues to spread until various peritoneal or other regions are involved, and disaster eventually follows. Because of this risk, pathologists and surgeons agree that whenever possible, ovarian cysts should be removed intact, through a sufficiently long incision even if it has to be extended to the costal margin. To make possible the safe use of a short incision, this instrument has been devised.* Its unique feature is the use of a ring of negative pressure to maintain a watertight junction between the smooth surface of the cyst and the flat surface of the attachment, which is less than two inches in diameter. A leak-proof channel carries a standard cannula and trocar size 22. While the apposed surfaces are hermatically sealed by means of the compressed rubber suction bulb, the trocar, with its cannula, is pushed into the largest cyst cavity. The point is than pulled up out of the way leaving the end of the

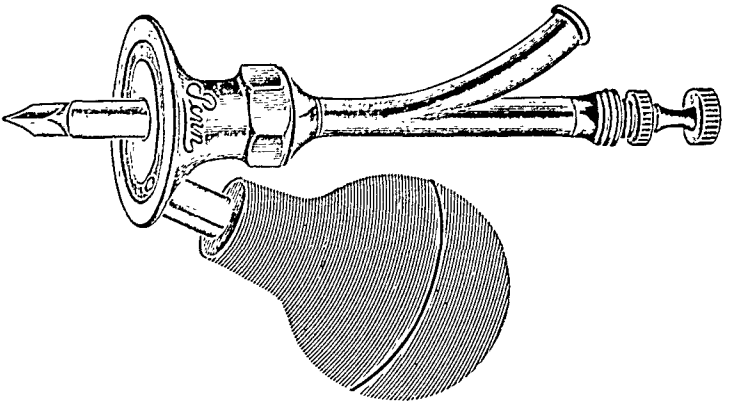


Fig. 1.

cannula protruding within the cyst cavity. By means of the usual suction pump, the fluid contents are aspirated through firm-walled rubber tubing into a large bottle. After a sufficient quantity has been removed, the collapsed sac with the apparatus still attached is then delivered outside the abdomen, ligated at its base and excised. If desired, the suction plate can be detached at any time after first applying firm clamps to the cyst wall from each side to keep in any remaining contents.

A possible advantage of this method is that there is no lifting of a large free mass out of the abdomen to cause a sudden relief of intra-abdominal pressure with consequent overfilling of blood vessels and the risk of cardiac embarrassment.

This method is not generally useful for (1) intraligamentary cysts or (2) cysts so adherent that they cannot be freely liberated. Good mobility is essential before applying the suction plate. It will fail occasionally when the cyst material is of such jellylike consistency that it will not flow through even the largest sized cannula, in which event the incision must be enlarged. Even in multilocular cysts of the more solid type, the emptying of one or more adjacent compartments by extending the trocar point through an intervening wall may produce an appreciable diminution in bulk and permit a shorter incision.

A recent operation at the Kensington Hospital for Women will illustrate the usefulness of this instrument:

Mrs. A. K., aged 52, noticed her abdominal enlargement for one year. Physical examination showed a large abdominal tumor hard and symmetrical and not freely movable because of its size. A midline incision, five inches long, revealed a right ovarian cyst about ten inches in diameter with smooth cyst wall and no evidence of

*Manufactured by the Penn Surgical Instrument Company, Philadelphia, Pa.

AN INSTRUMENT FOR THE SAFE DRAINAGE OF OVARIAN CYSTS

ADRIAN W. VOEGELIN, M.D., F.A.C.S., PHILADELPHIA, PA.

BEFORE presenting a new technique for the removal of large ovarian cysts, I would like briefly to mention a few facts about the two common types which comprise most of the large cysts coming to operation.

Falling into fairly distinct pathologic classes are the pseudomucinous cysts and the probably equally frequent serous or papillary cystadenomas. Of these, the gynecologist will encounter several in the course of a year and may recognize them as often by inspection as by palpation.

The first, the pseudomucinous cysts, grow quite rapidly and in former days were often allowed to reach mammoth proportions (the 100 or 200 pound tumors of the literature). They tend to be unilateral, freely movable and pedunculated. Commonly multilocular, one of the locules usually is larger than the rest. They contain a gelatinous fluid which is not true mucin; while usually benign, they sometimes show papillary overgrowth and may become carcinomatous. According to Goodall "pseudomyxomatous ovarian tumors as a class are generally looked upon with suspicion owing to the frequency with which they pass over into the malignant state."

However, these cysts occasionally terminate fatally in another way, namely the production of the weird condition known as "pseudomyxoma peritonei" resulting from spilling of the contents into the peritoneal cavity either by spontaneous rupture or at operation. Cell implantation and multiplication take place with the production of masses of pseudomucin. Peritoneal irritation, adhesions, lymphatic blockage, and eventually death result. Spontaneous regression seldom happens.

The other type of large ovarian cyst is the serous or papillary cystadenoma. It is slower growing but may also reach a large size. It may be unilocular but if multilocular, has fewer chambers with one large one predominating. The other ovary is frequently affected. The characteristic serous contents, clear or blood tinged, and the papillomatous infoldings or surface growths distinguish this tumor. All of these papilliform tumors are definitely to be suspected, as they tend to carcinomatous change. Even if primarily benign they lie at the borderland of malignancy. Unfortunately, microscopic study may overlook the carcinomatous area so that Ghon's rule is of practical value; namely "Any papillary tumor showing growth into its wall or implants externally, is malignant until proved otherwise."

In general, malignancy is proportionately more frequent in ovarian tumors than in neoplasms of any other organ. Metastases from primary malignant new growths of the ovary occur in from 85 to 90 per cent of all cases. Implantation metastases occur through the cyst wall or from spilling of the cyst contents into the peritoneal cavity either by rupture or at the time of an operation. Metastasis also occurs by direct extension or by way of the lymph vessels and glands. Blood vessel extension is relatively rare in ovarian malignancy.

However, let us leave the subject of cyst pathology and consider that of surgical removal. Modern technique has made ovariotomy a comparatively safe procedure. As ovarian tumors grow older and more prone to malignancy, they usually increase in size. The larger the cyst coming to the operating table, the greater is the temptation on the part of the surgeon to drain it by trocar and cannula, and then remove the collapsed cyst through an ordinary short incision. If this is done, we know that there *always* occurs spillage of cyst contents from around the trocar puncture into the peritoneal cavity. If the cyst is wholly benign or is not infected, no harm may result. Since, however, carcinogenic cells or pseudomucin-secreting

*Presented at a meeting of the Obstetrical Society of Philadelphia, November 3, 1938.

CASE 5.—No. A 71000. Brachypellic type pelvis, 10.25-11.5 cm. Unexplained persistent transverse presentation in patient beginning active labor. Classical cesarean section. Child 3,100 gm.

CASE 6.—No. A 73408. Small brachypellic type pelvis, 10.0-12.0 cm. Cervical cesarean section after trial of labor. Child 3,010 gm. Lateral roentgenometry during labor showed no attempt to engage fetal head. Patient of dystrophia dystocia syndrome type.

CASE 7.—No. A 48422. Platypellic type pelvis, 9.25-12.25 cm. Cervical cesarean section after short trial of labor. Child 3,765 gm.

CASE 8.—No. A 48838. Brachypellic type pelvis, 10.25-12.25 cm. Patient with rheumatic heart disease, mitral stenosis. No engagement of fetal head as shown by lateral view at term. Classical cesarean section. Child, 3,250 gm.

CASE 9.—No. A 63078. Small brachypellic type pelvis with narrow forepart, 9.5-11.75 cm. Lateral roentgenogram at term showed no engagement of fetal head and some evidence of disproportion. Cervical cesarean section. Child 2,880 gm.

CASE 10.—No. A 70230. Small brachypellic type pelvis, 9.5-11.5 cm. Trial of labor showed no advance or engagement of head. Cervical cesarean section. Child 2,785 gm.

CASE 11.—No. 60613. Small mesatipellic type pelvis, 10.25-10.5 cm. No attempt at engagement at term in pelvis relatively transversely contracted. Elective cesarean section. Child, 2,950 gm.

CASE 12.—No. A 18087. Average mesatipellic type pelvis, 11.25-12.00 cm. Primary uterine inertia. Irregular and ineffectual contractions over 48-hour period. Lateral view at end of this time showed head high above inlet. Dystrophia dystocia syndrome. Classical cesarean section. Child 3,170 gm.

CASE 13.—No. A 64612. Small brachypellic type pelvis, 10.0-12.0 cm. Lateral at term showed head not engaged. Patient with pregnancy toxemia. Elective cesarean section. Child 3,475 gm.

CASE 14.—No. 39681. Platypellic type pelvis, 9.0-13.0 cm. Elective cesarean section at term for evident disproportion. Child 3,260 gm.

CASE 15.—No. A 56652. Platypellic type pelvis, 9.0-12.75 cm. Evident disproportion at term with large baby. Elective cesarean section. Child 4,290 gm.

COMMENT

In six of the cases of this series, before the section was done a test of labor was given. In our clinic no definite rules govern this procedure. Patients must be carefully individualized and constantly supervised. In this connection the lateral roentgenogram has proved of notable service in reaching a decision between early operative intervention and a prolongation of the test. It is possible that two or three of the patients might have been delivered with difficulty by forceps or by version and extraction. We believe, however, as our knowledge of cephalopelvic relationships increases, that difficult vaginal deliveries, especially in so-called clean cases, will be greatly lessened. The toll of fetal deaths in such operations has received in the past too little attention.

MIDFORCEPS OPERATION

The midforceps operation was resorted to 18 times in the series, an incidence of 3.0 per cent. Most of these operations were done for cases of either high transverse arrest or high persistent occipitoposterior position.

implants. One hundred cubic centimeters of clear fluid were free in the abdominal cavity. The cyst trocar was applied to its surface and nine quarts of brown rather thick material evacuated without any spillage. After reduction, the cyst was easily delivered and the pedicle clamped and severed. Incidental removal of a hard left ovary was done. Convalescence was uneventful. The pathological report was as follows: Right ovary: Papillary cystadenoma showing many areas of carcinomatous change. Left ovary: Papillary cystadenoma.

The patient received postoperative x-ray therapy for good measure.

1521 LINDLEY AVENUE

DISCUSSION

DR. GEORGE W. OUTERBRIDGE.—This apparatus is an exceedingly ingenious and, I believe, efficient simplification of an instrument that was in vogue in Germany some twenty years or more ago for accomplishing the same purpose. It consisted, as I remember, of two concentric metal tubes, the outer of which was connected with a suction apparatus and placed against the cyst wall, sucked a collar of this around the inner tube through which was thrust the hollow trocar connected with a second separate suction apparatus for evacuation of the cyst contents. This was, of course, somewhat cumbersome in arrangement, and so far as I know was never very widely used. The apparatus presented would seem to accomplish the same purpose in a much less complicated manner.

DR. VOEGELIN (closing).—I did not know that this principle of suction had been used before. At first we thought that we could use one suction apparatus to maintain both the systems but found it could not be done successfully. That is why the use of the rubber suction bulb is necessary.

AUTOMATIC TRANSUTERINE TUBAL INSUFFLATOR*

OSCAR H. BLOOM, M.D., BROOKLYN, N. Y.

TRANSUTERINE tubal insufflation as a diagnostic procedure has become almost universal since the epoch-making work of Rubin and Stein. For complete safety to the patient during this test, any mechanism used for insufflation must fulfill the following requirements: (1) Deliver a fixed quantity of gas per minute, (2) the total quantity of gas injected should be readily measured, and (3) the apparatus must be equipped with an accurate manometer to measure the intrauterine pressure of the gas.

Not all the types of apparatus employed have these safety devices and the literature reveals several fatal accidents, as reported by Moench,[1] Kern,[2] Mansfeld and Dudits,[3] and Weitzman.[4]

To insure the greater safety of the patient, I have devised an automatic insufflator that has proved itself to be fool-proof. This machine has been in use for the past eight months at the Gynecological Clinic of Dr. M. N. Hyams, at the New York Postgraduate Hospital, as well as in private practice. About 100 insufflations have been done and the mechanism has met every expectation.

This instrument consists of the following parts:

1. A motor driven air pump, which is so constructed that it delivers 60 c.c. of air per minute. This rate is unalterable and beyond the control of the operator.

2. An electrically controlled time clock (*X*) which can be set to run from one to fifteen minutes and which shuts off the pump at the end of the time predetermined by the operator. Thus if the operator wishes to inject 180 c.c. of air, the time clock is set at three minutes and one can be positive that no more than that quantity will be injected.

*Presented at a meeting of the Brooklyn Gynecological Society, October 7, 1938.

3. A mercury manometer (*Y*) wired with electrodes that automatically shut off the pump when the mercury rises to the pressure that the operator believes to be dangerous. The upper electrode (*U*) is adjustable, and it is set at the desired height of pressure before starting the insufflation.

4. A light indicator (*I*) that tells the operator when the pump is operating, or when it is shut off, either by the time clock or the pressure control.

5. An electrical switch (*S*) for the house current.

6. A starting button (*B*) to actuate the pump.

7. An outlet (*O*) for the air to the patient.

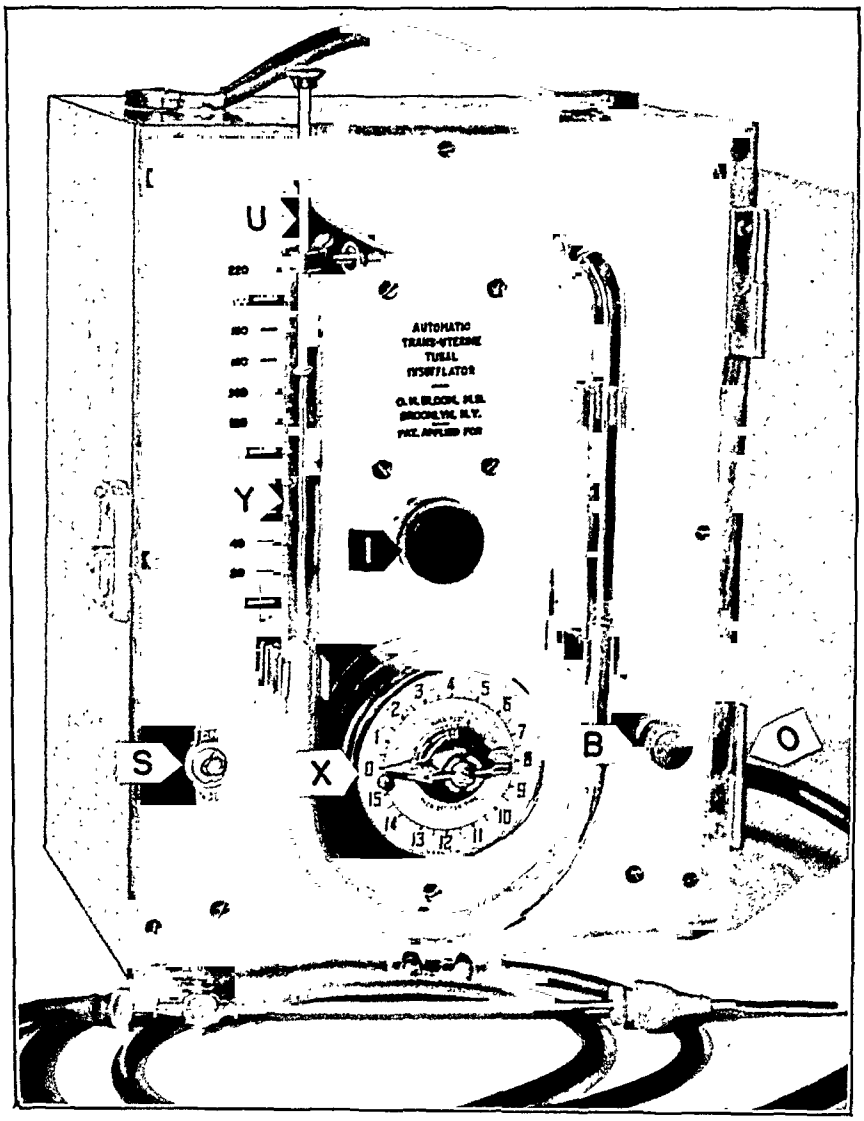


Fig. 1.

PROCEDURE

The patient is placed in a slight Trendelenberg position. The external genitals are scrubbed with tincture of green soap. The vagina and cervix are painted with mercurochrome. The cervix is grasped with a tenaculum and the Hyams' cannula is introduced into the cervical canal. Any nonirritating antiseptic solution may be introduced into the vagina to act as an indicator of air leakage from the external os.

The line switch (*S*) is thrown *ON*. The adjustable electrode (*U*) is set for any safe pressure, usually 140 mm. of mercury. The time clock (*X*) is set for three minutes in order to inject 180 c.c. of air, and the actuating button (*B*) is pressed.

The light indicator begins to glow and the operator knows that the air pump has begun to run. As the air begins to flow into the uterus, its pressure rises, as shown by the rise in the column of mercury in the manometer. If the tubes are patent, the apparatus will run for the allotted time (three minutes in this case) and then shut itself off, by means of the automatic time clock, thus insuring the injection of the quantity of air desired. However, in cases of complete stenosis, the mercury will continue to rise until it will make contact with the adjustable electrode (*U*), set at the safe pressure of 140 mm., and the pump will be shut off instantaneously, thus not allowing any more air to be forced into an already distended genital tract.

This automatic type of insufflator, which has been tried out in about 100 cases, will control: (1) The rate of flow of the air, (2) the total quantity of gas injected, and (3) the maximum pressure desired of the intrauterine gas.

REFERENCES

(1) *Moench, G. L.:* J. A. M. A. 89: 522, 1927. (2) *Kern, R. A.:* J. A. M. A. 86: 623, 1926. (3) *Mansfeld, O. P., and Dudits, A.:* Zentralbl. f. Gynäk. 58: 2117, 1934. (4) *Weitzman, C., and Cohen, M.:* New York State Med. J. 37: 1582, 1937.

Held, E.: A Clinical Study of Adnexal Tuberculosis, Gynéc. et obst. 35: 327, 1937.

The writer presents an analysis of 30 cases of adnexal tuberculosis observed during a five-year period and confirmed microscopically and bacteriologically, with an evaluation of the diagnostic methods employed. The fact is stressed that so frequently the diagnosis is only made at operation because the condition, though not uncommon, is not suspected.

Eleven patients had pleurisy preceding the pelvic condition by several years. Pleurisy and extrapulmonary tuberculosis are important in the history. Coincident or previous pulmonary tuberculosis was not common. In only three instances did tuberculous peritonitis of infancy precede the pelvic lesion. Contrary to Jayle's contention, there is no apparent tendency for gonorrhea and pelvic tuberculosis to coexist.

Sterility in the absence of a history of gonorrhea or postabortal infection should suggest the possibility of pelvic tuberculosis.

Little diagnostic value is attached to the blood picture and special tests such as Besredka's and Vernes'. Blood sedimentation is more rapid in tuberculous adnexitis than in the pyogenic variety and this acceleration is not uncommon in the complete absence of fever. Nevertheless, it is of no value in differential diagnosis. Salpingo-oophoritis of tuberculous origin responds in a very variable manner to pelvic diathermy. Poor response to this method of treatment cannot be considered as suggestive of tuberculosis.

Cul-de-sac puncture with guinea pig inoculation is advocated as a most useful procedure in the diagnosis of adnexal tuberculosis, even where mixed infection is present. This may be repeated several times and obviate the need for colpotomy which when done in the presence of tuberculosis sometimes results in fistulization.

Exploratory laparotomy is indicated when the diagnosis is not clear. It was performed by the author in six instances of his series.

ARNOLD GOLDBERGER

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

STUDY OF MATERNAL DEATHS IN CHICAGO

FRED L. ADAIR, M.D., AUGUSTA WEBSTER, M.D., AND LUELLA NADELHOFFER, M.D., CHICAGO, ILL.

THE Maternal Welfare Committee of the Chicago Gynecological Society studied maternal deaths in Chicago during 1934, 1935, and 1936. Each hospital delivering maternity cases was invited to have membership on this committee. Data were obtained by questionnaire and sent to the representative of the hospital in which the death occurred.

In 1936, the Board of Health cooperated in this study by supplying an obstetrician to investigate all maternal deaths by examination of the records and by interviews with the physicians in charge of the cases where possible. This material was then carefully studied by the Maternal Welfare Committee, and it was found that a large percentage of deaths appeared to have preventable factors.

It was therefore decided to invite interested societies to cooperate in plans to reduce maternal and infant mortality and morbidity.

The following organizations were represented: American College of Surgeons, Chicago Hospital Council and its administrative section, Chicago Medical Society, Infant Welfare Society, Catholic hospitals of the Archdiocese of Chicago, Chicago Pediatric Society, Chicago Gynecological Society, and the Chicago Board of Health.

As a result of this meeting a permanent committee was organized and named "The Joint Maternal Welfare Committee of Cook County." Dr. Fred L. Adair was chairman and Dr. E. L. Cornell secretary of this committee. Each organization was represented by two members.

Policies and procedures were formulated which were believed to be the minimum requirements essential in the conduct of a well-organized maternity division. These were in accordance with the highest scientific standards, but at the same time were practical enough to be easily applied in the average hospital.

The Chicago Board of Health, Herman N. Bundesen, President, then adopted "Regulations for the Conduct of Maternity Hospitals, Maternity Division of General Hospitals and Nurseries for the Newborn."

The regulations provided for complete physical separation of the maternity unit from the remainder of the hospital and for isolation facilities for the infected patient. They also required a well-equipped nursery for the care of the normal newborn, an isolation nursery, and a formula room. Special provisions were made for the care of premature and immature infants.

Minimum equipment for the maternity division was outlined including the essentials for the labor, delivery rooms, and nurseries.

Maternity hospitals were required to maintain personnel consisting of attending physicians, nurses and others adequate in training and numbers to carry on the proper routine and meet emergencies arising in such institutions. The work of the obstetric department was to be under the control of the obstetric staff—one of the members of which was to act as chairman of the department of obstetrics. He was to be a qualified specialist in obstetrics or obstetrics and gynecology. Each hospital was required to provide a competent obstetric staff for consultation and to control the obstetric procedures in the hospital.

Suggestions were made to the hospitals for the professional qualifications of the obstetric staff. Complete and detailed case records were required in all cases, including ante-partum and detailed hospital records.

Visitors in the maternity division were limited to two a day exclusive of the husband. Infants at no time were to come in contact with any visitors, and children under 16 years of age were excluded.

All operative procedures and medications were to follow generally accepted indications. The delivery rooms were to be conducted in strict accordance with surgical technique. The procedure of the personnel followed the concept that one who comes in contact with any patient should carry out aseptic technique before coming in contact with another patient. This precaution is especially important in connection with the care of parturient and puerperal women and newborn infants.

The majority of Chicago hospitals were cooperative and many willingly made many changes in their physical set-up and personnel in order to comply with these regulations.

It was evident, however, that in order to assure continued compliance periodic inspections would be necessary.

The Chicago Board of Health maintains a staff of physicians and nurses for this work. Monthly inspections are made, problems are discussed, and a written report is made in duplicate to the Board of Health and to the hospital administration.

Any difficulties or differences in interpretation or application of the regulations are referred to the Joint Maternal Welfare Committee of Cook County which acts in an advisory capacity to the Board of Health of the City of Chicago and as a liaison committee between doctors, hospitals, and the Board of Health.

INFORMATION CONCERNING NEW STANDARD CERTIFICATE OF LIVE BIRTHS AND NEW STANDARD CERTIFICATE OF STILLBIRTHS

THE American Committee on Maternal Welfare has pointed out the great need for additional medical information with respect to all births (live and still). For the reduction of mortality connected with birth, accurate information must be available with respect to prenatal and natal conditions. This information is necessary not only for the reduction of fetal and infant death rates, but also for the reduction of the maternal death rate and for the improvement of maternal and child health.

The committee has called attention to the magnitude of the loss of life connected with pregnancy and childbirth. The total loss from these causes in 1935, as shown by the Bureau of Census figures, was 161,249 lives, including 14,296 maternal deaths (12,544 deaths assigned to pregnancy and childbirth, and 1,752 deaths in which pregnancy or childbirth was a complicating factor), 77,119 stillbirths, and 69,834 infant deaths in the first month of life, of which 56,262 were due to prenatal and natal conditions.

Official State health agencies are urged to adopt the new standard stillbirth and birth certificates including supplementary data.

Uniform reporting of stillbirths throughout the United States can only be made possible when every State has adopted a standard certificate of stillbirth and has accepted the American Public Health Association definition of stillbirth, i.e., a stillborn child is one which shows a complete absence of life, no breathing, no action of heart, no movement of voluntary muscles.

The supplementary data for all live birth certificates referred to above is as shown in Chart 1.

Chart 1.

Suggestions by Children's Bureau for optional items to be carried at the bottom of the Birth Certificate.

Supplementary data below are not a part of the legal certificate.	
29a. *Pregnancy*, Complications of:_____	d. Did baby have any: _____
_____	(1) Congenital malformation? _____
b. *Labor*, Complications of:_____	Describe: _____
_____Induced? _____	(2) Birth injury? _____Describe: _____
c. Was there an operation for delivery?_____ yes or no	e. Was a prophylactic drug used in the baby's eyes? _____ If "yes" state drug _____ yes or no
State all operations _____	

As no standard certificate of stillbirth has ever been issued by the Bureau of Census prior to this year, and as only seven States have a stillbirth certificate at the present time, the portion of the standard stillbirth certificate giving information in addition to that received from all births is printed in Chart 2.

Chart 2.

Certificate of Attending Physician or Midwife

25. Did child die before labor?_____	29. Cause of stillbirth (State only morbid conditions causing fetal death. Do not use such terms as prematurity, asphyxia, etc.)
during labor? _____	a. Fetal causes: _____
26. *Pregnancy*, complications of: _____	_____
27. *Labor* (a) Complications of: _____	b. Maternal causes: _____
_____ (b) Induced? _____	_____
28a. Was there an operation for delivery?____ yes or no	30. I hereby certify, that I attended the birth of this child, who was born dead at the hour
b. State all operations, if any_____	of _____ M. on the date above stated.
_____	Signature _____ Title_____
c. Did child die before operation?_____	Address _____
or during operation? _____	_____
31a. Burial, cremation, or removal _____	33a. Statement of local registrar or coroner if physician was not present at stillbirth._____
31b. Place_____ \| 32c. Date: _____ Month day year	_____
32a. Signature of person burying the body _____	33b. Signature _____ Title_____
32b. Address _____	34. Registrar's own signature_____
	35. Date filed with local registrar_____

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 6, 1938

The following papers and case reports were presented:

Management of an Institutional Outbreak of Infectious Diarrhea of the Newborn Infant. Drs. R. L. Roddy, J. S. Forrester and H. Landow. (By invitation.) (For original article, see page 1037.)

X-Ray Localization of the Placenta by Soft Tissue Technique and Without the Use of Opaque Media. Dr. R. Manges Smith. (By invitation.)

Implantation of Ovary in the Uterine Cornu. Dr. Margaret C. Sturgis. (For original article, see page 1048.)

MEETING OF NOVEMBER 3, 1938

The following papers were presented:

An Instrument for the Safe Drainage of Ovarian Cysts. Dr. Adrian W. Voegelin. (For original article, see page 1053.)

Syphilis in Relation to Gynecology and Obstetrics, With Special Reference to Diagnosis and Treatment. Dr. John A. Kolmer. (By invitation.)

Arsenical Treatment Reactions Among Syphilitic Pregnant Women, With a Report of Seven Maternal Deaths From Syphilis Therapy. Dr. Norman R. Ingraham. (By invitation.)

MEETING OF DECEMBER 1, 1938

The following case report and papers were presented:

Brain Tumor Complicating Pregnancy. Dr. Bernard Mann. (For original article, see page 1051.)

The Effect of the Female Hormones and of Pregnancy Upon the Ureters of Lower Animals as Demonstrated by Intravenous Urography. Drs. Franklin L. Payne and Philip J. Hodes. (For original article, see page 1024.)

The Therapeutic Value of Low-Dosage Irradiation of the Pituitary Gland and Ovaries in Functional Menstrual Disorders and Sterility. Drs. Charles Mazer and George Baer. (For original article, see page 1015.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 21, 1938

The following papers were presented in a symposium on Rare Ovarian Tumors:

1. **More Recent Developments in Ovarian Tumors.** Dr. Walter Schiller (by invitation).

2. **Arrhenoblastomas.** Dr. A. E. Kanter. (Published elsewhere.)

3. **So-Called Lutein Cell Tumors.** Dr. Otto Saphir (by invitation). (For original article, see page 1008.)

4. **Variations of Lipoid Content in Certain Ovarian Tumors.** Drs. R. B. Greenblatt, J. P. Greenhill, and W. R. Brown. (For original article, see page 929.)

MEETING OF NOVEMBER 18, 1938

The following paper was presented by invitation:

Hormone Factors in the Toxemias of Pregnancy. Dr. Howard C. Taylor, Jr. (For original article, see page 963.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 4, 1938

The following paper was presented:

Fetal and Neonatal Disease and Death. Dr. Fred L. Adair and Edith L. Potter, Chicago, Ill. (By invitation.) (For original article, see page 993.)

MEETING OF OCTOBER 7, 1938

The following papers were presented:

Automatic Transuterine Tubal Insufflation. Dr. Oscar H. Bloom. (For original article, see page 1055.)

Primary Ovarian Pregnancy. Dr. Harris M. Rabinowitz.

A Ten-Year Study of Ectopic Gestation at Beth-El Hospital. Drs. Nathan Reibstein, Samuel Weiner and Harris M. Rabinowitz.

The Interposition Operation. Drs. Oscar M. Bloom, Abr. Heinrich and Abr. Koplowitz.

Ruptured Interstitial Pregnancy in the Fourth Month. Dr. Philip Oginz.

A Modified Sturmdorf Operation for Vesicovaginal Fistula. Dr. Abraham Koplowitz. (For original article, see page 1045.)

Ten Years of Obstetrics at the Beth-El Hospital. Drs. Wm. Levine, Harry Warwick, H. Warwick and P. Oginz.

MEETING OF NOVEMBER 4, 1938

The following papers and case reports were presented:

Diabetes in Pregnancy. Dr. Martin M. Shir. (For original article, see page 1032.)

Pelvic Examination in Suspected Placenta Previa. Dr. Stanley C. Hall.

The Criteria and Significance of Engagement. Dr. Arthur S. MacGregor.

What Is a Test of Labor? Dr. Frank P. Light.

The Postmature Fetus. Dr. John Casagrande. (For original article, see page 1028.)

"Once a Cesarean, Always a Cesarean." Dr. G. R. MacLachlan.

MEETING OF DECEMBER 2, 1938

Massive Intraperitoneal Hemorrhage Resulting From Rupture of a Superficial Vein of a Uterine Fibromyoma. Dr. Anthony L. Shelfo. (For original article, see page 1049.)

Granuloma Inguinale (Venereum). Drs. Samuel A. Wolfe and Eugene J. Tortora.

The Etiology and Treatment of Endocervicitis and Cervical Erosion. Dr. Anthony Wollner. (For original article, see page 947.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Analgesia and Anesthesia in Labor

Minnitt, R. J.: Analgesia in Midwifery, Brit. M. J. 2: 538, 1937.

The author outlines the present methods for obtaining analgesia in labor. Two main types are available: (1) drugs given orally or hypodermically, and (2) inhalation analgesia.

The apparatus and technique are described whereby the patient feeds herself a gas and air mixture (nitrous oxide) with each pain during the first and second stages of labor.

Maternity nurses receive special training along these lines of procedure, and specially trained candidates in gas analgesia receive certificates to that effect.

Gas and air analgesia is contraindicated in abnormal cases, i.e., cardiacs, phthisis, bronchitis, albuminuria, and hypertension.

The demands of the parturient for the best relief of labor pains are gaining wider recognition and drug therapy is giving place to gas analgesia.

F. L. ADAIR AND S. A. PEARL.

Bonar, Barnet E., and Blumenfeld, Charles M.: Obstetric Anesthesia, Surg. Gynec. Obst. 66: 179, 1938.

There is need for greater use of precise methods to determine the effect of anesthetics and analgesics on uterine contractions and on the fetus. As far as the uterus is concerned hysterography is the method of choice at present. Especially is this true of external hysterography since it is reasonably accurate, simpler, safer for the patient, and less subject to criticism. A procedure recently described by Rosenfeld and Snyder offers great possibilities in studying the effects of anesthetics and analgesics upon the fetus. Experiences with this method are related and the observations of Rosenfeld and Snyder regarding the existence of apparently physiologic intrauterine fetal respiratory movements which are depressed or stopped by some of the anesthetics and analgesics are confirmed. There is evidence that this method may be of value in studying the effects of these agents upon uterine contractions also. Direct and color motion picture observations upon animals anesthetized by cord transection are reported and the advantages and disadvantages of the method are discussed. In order to obtain more accurate data there is need for an instrument which will record these movements graphically. It is possible that this may be accomplished in the near future by using an instrument recently devised by Fenning to record graphically small changes of volume. Further studies along these lines are being pursued.

WILLIAM C. HENSKE.

Wolf, Willi: The Cause of Pain in Labor and Its Significance for Conduct of Delivery, München. med. Wchnschr. 85: 824, 1938.

Wolf discusses labor pains and their probable causation. From clinical observation he has come to the conclusion that real pain in active labor is caused by the dilatation of the internal os and of the external os, and that because of this it is easier to explain all painful and painless processes in pregnancy, labor, and the puerperium than by the theory that the pain is due to uterine contractions. Furthermore he feels that this new theory has possibilities which are of some importance also for the management of labor and delivery.

C. E. PROSHEK.

Paton, M. Donald: A Study of a Few Common Types of Obstetric Analgesia, Texas State J. Med. 33: 506, 1937.

In the experience of Donald M. Paton (Houston) morphine-scopolamine, scopolamine-sodium amytal, and nembutal-scopolamine, when properly used, give satisfactory amnesia in 80 per cent of cases. These drugs do not increase the incidence of operative delivery, and danger to the baby is negligible in the hands of one trained in the use of these analgesics. Nembutal seems to be safer than twilight sleep or sodium amytal with scopolamine. Twilight sleep used in a toxic patient may provide a definite threat to the life of the baby. Nembutal can be started a little earlier in labor than twilight sleep or scopolamine-sodium amytal and is therefore perhaps preferable to them in multiparas.

J. P. GREENHILL.

Bell, Warren W.: Experiences With Scopolamine in Obstetrical Practice. Reasons for Its Discontinuance by the Author, West. J. Surg. 46: 276, 1938.

The writer analyzes his experience with 441 patients within a period of between two and a half and three years. Of the total number 225 had been given scopolamine and 216 nembutal. He found that scopolamine usually is effective in producing a desirable degree of amnesia and analgesia, but that its cumulative effect upon the respiratory center of the infant so often results in asphyxia that he has not felt justified in continuing its use. Although dangers of scopolamine to the life of the mother may usually be eliminated, Bell is convinced that neither the mother nor he, as practitioner, can justify its use merely in an endeavor to minimize the suffering of the mother in childbirth.

The experience with 216 patients to whom nembutal was given has convinced the author that the barbiturates are not only as effective as scopolamine, but that they are far safer for both mother and child.

J. P. GREENHILL.

MacPhail, Gray, and Bourne: Pentothal Sodium as a Hypnotic in Obstetrics, Canad. M. A. J. 37: 471, 1937.

They gave pentothal sodium to 238 women in labor without any noticeable harmful effects to either mother or child. It appeared that, unlike ordinary barbiturates, this thio-derivative did not cause excitement at any time. Furthermore, the hypnotic action of pentothal sodium appeared to be attended by a marked degree of amnesia. One of the conclusions reached was that labor was shortened in duration. The method of administration was to give capsules by mouth, 4 gr. being allowed as soon as pains were definitely established, 3 gr. being repeated half an hour later, and again at the end of one hour. If required, 2 to 3 gr. might be repeated every half hour to one hour if the effects seemed to be wearing off.

Scopolamine, 1/100 to 1/150 gr., was given at the time of the first dose. Pentothal sodium may also be given in solution per rectum. The dose used was 7½ gr. dissolved in 25 c.c. of water and repeated in an hour's time. A further series of 120 obstetric cases were treated in this manner and the results were quite satisfactory.

J. P. GREENHILL.

Siegler and Beris: Evipal Soluble Rectally Applied in Obstetrics. A Preliminary Report, New York State J. M. 38: 1071, 1938.

Evipal soluble was used. Supplied in ampules of 3 gm. This amount was dissolved in 90 c.c. of distilled water and applied rectally. To women weighing less than 150 pounds 30 c.c. (1 gm.) of solution was administered, to women weighing over 150 pounds a larger dose of 45 c.c. (1.5 gm.).

The authors believe that evipal soluble is a safe analgesic and amnesic to be used rectally in obstetrics. There are no deleterious effects on either the par-

VERSION AND EXTRACTION

Version and extraction was used as a method of delivery 4 times or in 0.66 per cent of the cases. These are briefly summarized as follows:

1. High transverse arrest in average brachypellic type pelvis (11.25-13.5 cm.) after fourteen hours of hard labor, 3,460 gm. child delivered without difficulty.

2. High transverse arrest in small brachypellic type pelvis (10.0-12.0 cm.). A difficult extraction after 22 hours of labor resulting in the stillbirth of a 4,059 gm. fetus. Low cervical section should have been performed (see comment in fetal mortality résumé, Case 9).

3. High transverse arrest in average brachypellic type pelvis (11.5-12.75 cm.) after 22 hours of labor, child, 3,755 gm.

4. Primary uterine inertia, prolonged labor. High arrest. Small mesatipellic type pelvis (10.5-11 cm.). Child 3,350 gm.

FETAL MORTALITY

There were no maternal deaths but there were ten fetal deaths in this series. These are summarized as follows:

CASE 1.—No. A35496. Aged 27 years, average brachypellic type pelvis, 10.75-12.75 cm. Normal spontaneous birth after 22 hr. labor. Fetal heart never heard during labor and fetus showed signs of maceration. Patient's Wassermann and Kahn reactions negative early in pregnancy, but there was later discovered a questionable history of syphilis before marriage.

CASE 2.—No. 57772. Aged 25 years, small brachypellic type pelvis, 10.0-12.0 cm. Low forceps completed a 9½ hour labor. Macerated fetus, fetal heart never heard during labor. Wassermann reaction negative.

CASE 3.—No. AS0653. Aged 17 years, average mesatipellic type pelvis, 11.25-12.25 cm. Breech extraction of stillborn hydrocephalic monster with spina bifida. Fetal heart never heard during labor.

CASE 4.—No. 55110. Aged 23 years, small mesatipellic type pelvis, 11.0-11.75 cm. Difficult forceps extraction of stillborn monster with hydrocephalus, spina bifida and club feet.

CASE 5.—No. A51510. Aged 24 years. Average mesatipellic type pelvis, 12.25-13.0 cm. Spontaneous delivery 2755 gm. child which breathed poorly from the first. Respiratory rhythm grew rapidly worse and physical examination showed complete atelectasis on the right. Child died twenty-four hours after birth. Diagnosis: Bilateral pulmonary atelectasis.

CASE 6.—A58171. Aged 20 years, small mesatipellic type pelvis, 10.0-11.0 cm. Labor induced for pre-eclamptic toxemia. Prolonged labor, thirty-two hours, fetal heart not heard toward end of second stage. Low forceps extraction of 2,727 gm. child which could not be resuscitated. Comment: Prolonged labor in toxemia of pregnancy the probable cause of intrauterine death.

CASE 7.—No. 86933. Aged 21 years, average brachypellic type pelvis, 11.0-13.0 cm. Breech extraction of 3,510 gm. child from L. S. A. Duration of labor 22¾ hours. Resuscitation not possible although operation not apparently difficult. Comment: Fetal death probably due to the technic of the procedure.

CASE 8.—No. 68618. Aged 17 years, average mesatipellic type pelvis, 11.5-12.5 cm. Breech extraction of 3,400 gm. child after twenty-eight hours of labor. Comment: Delay in extraction due to extended arms the cause of fetal death.

CASE 9.—No. 93549. Aged 18 years, average brachypellic type pelvis, 11.25-13.0 cm. Twenty-five-hour labor in obese patient with uterine inertia. Midforceps

were unaffected by morphine, nitrous oxide-oxygen, the barbiturates, cyclopropane, ether and chloroform. The strength of the uterine contractions, markedly reduced by ether and chloroform, was unaffected by the other anesthetics. All of the above drugs reduced the contribution of the abdominal muscles to the intrauterine pressure.

During labor pains the systemic blood pressure increases and the pulse pressure widens. The effective maternal arterial pressure to the placenta diminishes—sometimes to zero. The pressure which irrigates the placenta is increased by obstetric anesthetics and by epinephrine.

J. P. GREENHILL.

Cameron, G. R.: Some Recent Work on Barbiturates, Proc. Royal Soc. Med. 32: 309, 1939.

Toxic effects are sometimes seen after administration of quite small amounts of barbiturates. This is a matter of almost universal experience. The quick acting members of the group, nembutal and evipan sodium, are more frequently concerted than the slow acting forms, such as barbital sodium and phenobarbital sodium. The liver is not infrequently and permanently damaged by prolonged administration of nembutal. There is a feeling among clinicians and pathologists that it is not wise to give barbiturates, even in small doses, to subjects with liver disease.

HUGO EHRENFEST.

Casalta, E.: Accident from Spinal Anesthesia in a Low Cesarean Section, Bull. Soc. d'obst. et de gynéc. 27: 437, 1938.

The author reports a sudden death from spinal anesthesia which occurred while the uterine incision was being closed at the time of a low cesarean section. This is the first accident of the kind encountered by the author. He mentions other similar deaths reported by Cotte and Bansillon, and by Brochier and Ambre.

J. P. GREENHILL.

Cambon: Low Cesarean Section and General Anesthesia. Preventive Procedure for Control of Bleeding, Bull. Soc. d'obst. et de gynéc. 27: 440, 1938.

Cambon has given up the use of spinal anesthesia for cervical cesarean sections, because he encountered a sudden death due to it, because his colleague, Plasse, also had a similar accident and because he knows of a few other sudden deaths from spinal anesthesia which have not been published. Hence Cambon believes that spinal anesthesia is more dangerous than ether and he now uses ether. For the control of bleeding he injects pituitary extract directly into the uterine muscle and also ergotamin subcutaneously.

J. P. GREENHILL.

obstetric cases with a feeling of confidence, convinced that the main thing to do was to give nature a chance. This may be the reason why I never lost a mother.

The mothers' ages ranged from 13 to 52 years. The average number of children to each mother was about a dozen; there were few with less than six, and in two families I attended the twenty-first and twenty-second confinements, respectively. There were very few stillborn children.

Of course, I had experience with all the normal fetal positions as well as with many abnormal, or undeliverable, presentations, in which it was necessary to use the appropriate operative procedures. There were quite a number of shoulder presentations, which I delivered by turning, usually under ether, but in quite a few cases without any anesthesia. One patient had twelve breech presentations, one shoulder presentation, which I turned, and one normal cephalic presentation. I can recall two face presentations. The first, with the chin forward and to the right, gave no trouble other than a prolonged period of delivery. In the second case, the chin was to the left and posterior. The patient was 32 years old, and this was her first baby. I was called by telegraph at nine in the evening, and reached the home, 25 miles distant, by daylight the next morning (horse and buggy days). The bag of waters had ruptured, and most of the fluid had escaped, but there was no dilatation and with each pain there was a further loss of fluid. By that evening, the patient was becoming impatient, and I suggested consultation. It was not until 11:00 P.M. that the consultant arrived. He thought it would be best to turn, but I told him that there was practically no water left in the uterus and that it would be impossible to turn under such circumstances. Nevertheless, he insisted upon trying and, with the consent of the patient, made the attempt, but found that he could not even introduce his hand into the uterus—there was too little dilatation. Then he wanted to introduce forceps and deliver instrumentally, and the husband asked him to try. I demurred and told him it would be dangerous, but in spite of this he went ahead. Naturally, he failed even to introduce the blades, and then gave it up for a bad job and went home. By morning I was able to diagnose a chin posterior, which is ordinarily not deliverable. The only other procedure, except to give nature more chance, was craniotomy, which was refused. Exactly at noon, the head adjusted itself so that the chin was in the anterior position, and in a short time the baby was born. The child was dead, but the mother made a good recovery and the next time had twins. I forgot to say that this first baby weighed 12 pounds at birth.

All of these deliveries were conducted in town or farm homes. In those days, physicians did not look upon childbirth as a disease, but rather as a physiologic process which should be treated accordingly, unless there were complicating conditions. The water supply was usually from surface wells, rarely from cisterns, and light was obtained from a candle or kerosene lamp. A doctor was expected to be able to pass a catheter without exposing the patient. I can still do it. There were no indoor bathrooms, and the toilets were the old-fashioned privy vaults. Instead of toilet paper, it was quite customary to use corn cobs. In the whole of Sioux County, I knew of but one bathroom.

The great bulk of the people were then able to pay the standard obstetric fee, which was $5.00 in town and $10.00 in the country, regardless of time or distance. The longest trip I made to attend a confinement was from Alton, in Sioux County, to Alvord, in Lyon County, a distance of fully fifty miles.

If I were to practice obstetrics now, I would refuse to attend a patient anywhere else than in the home. Patients become immune to any bacterial organisms in their own homes, whereas, even in the best regulated hospitals there are of necessity a great variety of organisms from many sources.

There was no prenatal care. Sometimes the husband or, more rarely, the wife would drop in at the office to advise me about the date of the coming event and to urge me to come quickly when I received a call. Patients did not report for examination or bring urine specimens for testing. It was only when edema complicated the pregnancy that we called for some urine and examined it for albumin and casts. Blood pressure appliances were not yet in use, and bacteriology was still in its infancy.

Correspondence

Rural Obstetric Practice a Generation Ago

The following letter was received recently from Dr. Ferdinand J. Smith, of Milford, Iowa, in response to a general appeal to the physicians of the State for assistance in compiling data on home deliveries. It occurred to the recipient that Dr. Smith's letter was of too much historic value to justify its burial in a filing cabinet, and consequently permission was sought to publish it after a few minor alterations. This request was graciously granted, and the Editor of the JOURNAL offered his cooperation.

E. D. PLASS.

Milford, Iowa
April 29, 1938.

My dear Doctor Plass:

I have recently received your letter and the enclosed questionnaire, but cannot be of assistance to you since I am no longer in practice, although I have records of over four thousand confinement cases attended during my professional life. There are, however, certain data which I can give you from memory in the hope that they may be worth while.

I was graduated from the Medical Department of the State University of Iowa on March 2, 1887, after three courses of lectures of four months each. My undergraduate, practical experience in the office of Dr. W. F. Peck, then Chief Surgeon of the Rock Island Railroad and Dean of the Medical Department at Iowa City, was limited to surgery. I did not see the ordinary diseases of childhood, lung fever, typhoid fever or, in fact, any other internal medical cases until I began to practice medicine. The only obstetrics I saw was what the Professor of Obstetrics, Dr. J. C. Schrader, demonstrated on a manikin, which was, I suppose, better than nothing.

The majority of my obstetric deliveries occurred between the time of my graduation and January, 1904, when I was appointed full-time Professor of Chemistry and Dean of the Junior College of Medicine at Drake University, Des Moines. I remained in these positions for several years, but during the vacation periods had a small obstetric practice near Lake Okoboji where I spent the summers. In June, 1913, I resumed the practice of medicine and until 1919 was very active, especially in obstetrics. During this period, there were two days, on each of which I attended five confinements. From 1919 I lived at my home on Lake Okoboji and for some years did considerable practice, but gradually began to taper off and am now retired.

I still remember my first obstetric case. I arrived at the patient's home, examined her but failed to locate anything, and then began to get excited, since I did not seem to get anywhere. Finally I decided it was foolish to worry. Why worry? The mares, the cows, the ewes, all the farm animals had their offspring without assistance and got along fine. In good time, I was able to locate the presenting part and to determine the position and was gratified to find it normal. By continuing to exercise masterly inactivity, the baby eventually arrived, as big as life and twice as natural. After severing the cord, I watched the old neighbor lady wash and dress the baby, and assisted her in dressing the cord. I was beginning to think about going home when she suggested to me that it might be a good time to remove the afterbirth. I was very glad that she spoke of it but did not tell her so, because I had forgotten all about it. On examination I found the placenta in the vagina and removed it easily. After this experience, I went to my

there is too much chance for infection in hospitals. Perhaps the fact that too many of the mothers or (and) fathers have been infected with venereal disease may contribute to the present higher death rate. Such complications were not common in the country when I was practicing.

One case, which I had, was rather unusual: a Dutch woman, only recently over from Holland, gave birth to a baby on a Saturday night. I saw that there was another one coming and waited quite a while, but finally decided to go home and wait until I was called. A week from the following Monday, the patient did a large washing and that night I assisted her with the birth of the second baby. She made a good recovery. Another patient, a primipara, attended a neighborhood party the day after her baby was born and took part in the dancing. If the experience hurt her in any way, there was no evidence of it.

I have left the most unusual case I ever saw for the last. I was called by a man who said that his wife had given birth to a baby some hours before, and that the two old ladies who had cared for her had advised him to obtain the services of a physician as quickly as possible because she looked terribly ill. I went with him immediately and when we came to the home I could see that she had been bled white. There was no pulse at the wrist and only very feeble heart sounds were audible with the stethoscope. It was evident that she was about to die, so I told him that she was beyond the benefit of any treatment and that, if he and his wife had anything to say to each other, it should be done quickly. Instead of complying, he ran out and told his boys to get on horseback and to bring back as many physicians as they could find. When he returned to the house, his wife was dead. The two old ladies told me that they had repeatedly suggested to the patient that she have a doctor, but that she had insisted that the pains were not yet sufficiently strong. Finally, she had one terrific pain, the most agonizing they had ever seen, during which the head was born. There were no more pains, but the two old ladies extracted the rest of the child by drawing the head down until the body was delivered, and then cut the cord. The two ladies went to another room to wash and dress the baby, and then went back to see how the mother was getting on. They found her looking terribly bad and immediately had the husband come for me. The child, which was the patient's twelfth or thirteenth, weighed 21 pounds and is still living. She was not more than average in size and was the mother of quite a bunch of children. What happened, of course, was a rupture of the uterus with hemorrhage into the abdominal cavity. I think that this was a case of carrying a child much past the normal time.

Now, Dr. Plass, this is probably not exactly what you want, but on the other hand it is. These people had as good care, perhaps better, than most mothers have now, because the physiologic processes were allowed to go on without interference, and it is after all the duty of the physician to allow nature every opportunity to do its own work in its own way. It is wonderful how an overly large head and a small birth canal, if given plenty of time, will conform to each other with a resulting normal delivery.

Remember, too, that in all these confinements I had consultation only four times, the balance were taken care of by myself with such assistance as was available in the home or in the immediate neighborhood. Doctors were few and far apart and, since each had his own work to do, we became accustomed to taking the entire responsibility upon ourselves. The roads were atrocious, only dirt roads, and sometimes next to impassable. I did most of my traveling on horseback with a saddle bag for medicines and instruments. I would start out in the morning, make a round trip, and frequently on getting home would find other work waiting for me. If I were a young man again, I would set myself up as a specialist in obstetrics, although I fear that the modern mother would not approve of my ways. I believe that many obstetric difficulties would disappear if our women would develop their muscles from childhood up by suitable housework—doing the family laundry, scrubbing, and other heavier tasks.

I am too old to take up the practice of medicine any more: it is now nearly 52 years since I left Iowa City and engaged in practice. I was a general practi-

In my first cases of puerperal eclampsia (six months after I began practice), I used large doses of morphine hypodermically, to reduce the convulsions, and hot packs. The baby was born prematurely and eclampsia did not develop until four hours after delivery. The patient made a good recovery. All of my other puerperal convulsive patients were treated with Norwood's tincture of Veratrum viride, 15 minims hypodermically, repeated every thirty minutes until the pulse rate was 55 to 65 per minute. At the same time the patient was wrapped in a cotton flannel blanket wrung out of hot water, and ear corn, taken out of boiling water, was placed down both sides of the patient's body outside the blanket and under the quilt. This was continued until the edema was very much lessened and, in some cases, this result was achieved in no more than thirty minutes. It was rare that there were any more convulsions after such treatment. I had 18 or 20 eclamptic cases in my own practice and in consultation with other physicians, and did not lose a single mother. If treatment was begun early enough, the child also usually survived. (A paper on this subject was presented before the Northwestern Iowa Medical Society, April 30, 1919, and was published in the *Journal of the Iowa State Medical Society*, in August, 1919.)

The great bulk of my deliveries were spontaneous: among more than 4,000 cases, there were not over 30 instrumental deliveries. Once, I used the instruments on an aftercoming head, for fear that the baby might be asphyxiated. When I did use forceps, I produced traction with only two fingers, having found that this maneuver gave the patient much relief from pain by relieving the uterus of part of its muscular labor. I never gave anything to increase the activity of the uterus before delivery, except in certain cases where my experience indicated the liability of a relaxed uterus with consequent hemorrhage. In these instances, I gave a capsule containing 10 gr. of quinine sulfate immediately before birth. If this had not been done and hemorrhage appeared, I applied cloths wrung out of freshly drawn well water over the lower abdomen, and gave a teaspoonful of fluid extract of ergot. Perineal wounds were repaired immediately with catgut sutures. A wash boiler half full of boiling water served to sterilize dishes, old muslin and towels and also provided a supply of sterile water. There were no rubber gloves available, but I washed my hands thoroughly with soap and hot water, used a nail brush carefully, and sometimes immersed my hands in a solution of permanganate of potash. The vulva was not shaved.

Vaginal examinations were made only when indicated to follow the course of labor or to explain the cause for delay. Examinations per rectum had not yet been introduced. If an anesthetic was used, it was not given until the head engaged the perineum and was employed then only to safeguard the perineum. Ether was the usual anesthetic and was generally administered by one of the old ladies, or, perhaps, by the husband. On one occasion, I had the hired man give the ether, because the husband would not do it and no old ladies happened to be available. Unless there was a bronchial condition contraindicating its employment, I always felt safe in using ether. When there was evidence of bronchial involvement, I would either dispense with an anesthetic entirely or would give chloroform myself. Many labors, even those with the first child, were terminated within eight hours, particularly in women having a lanky build, whereas plump women usually had a harder time of it in their first labors. Faulty, even though not abnormal, positions led to more severe first labors than if the fetus were in a more normal position. As a rule, the second child came more easily, the third one much more so, and after that it was nip and tuck between the stork and myself. My patients were almost entirely of German and Dutch extraction. I was much impressed by the fact that most of the mothers were comparatively youthful looking. In certain large family groups it was difficult to pick out the parents from the older children.

In those days there were no trained nurses, but the older women, who had arrived at the end of their childbearing, would help out their younger neighbors. And they acquitted themselves well. *They did as they were told without question.*

Every one of my living babies was blessed with a living mother. And I was not the only doctor who had such an experience. It is my personal conviction that there is altogether too much meddlesome midwifery on the part of physicians, and that

'Swiss-cheese' pattern, and finally to the markedly proliferative hyperplasia pictures which may even closely resemble cancer.'' (This is an exact quotation from our paper.)

If one considers the causation of hyperplasia, it is not at all paradoxical, strange though it seems to be to Dr. Herrell, that it may be associated with amenorrhea, menorrhagia or sterility, though no one now ''blames'' the endometrial lesion for any of these symptoms of the underlying endocrinopathy.

No one can take exception to his description of the menstrual phases, which is essentially what has been accepted for the past quarter of a century or more, though Dr. Herrell seems to like the term ''differentiative'' rather than the more generally used terms ''luteal'' or ''secretory.'' It is gratifying to us, too, to note that he has fully confirmed our own findings that proliferative endometrial activity is not uncommon in postmenopausal women, and that such postmenstrual endometrial proliferative pictures are frequently associated with adenocarcinoma. This was the whole point of our paper, and Dr. Herrell seems to have missed it quite completely. This is not the place to discuss a number of other points in Dr. Herrell's paper, such as the interpretation of some of the microscopic findings (I feel sure, for example, that most gynecological pathologists would consider the picture in Fig. 11 perfectly benign and not typical adenocarcinoma Grade I), but I did want to get the record straight as to what we tried to show in our own paper, as this would not be apparent from Dr. Herrell's reference to it.

EMIL NOVAK, M.D.

26 East Preston Street
Baltimore, Md.
April 13, 1939.

To the Editor:

If my answer to Dr. Novak's letter is brief, my intention is not to be curt. However, I believe my answer is contained in the paper to which Dr. Novak objects.

In the first two paragraphs on page 564 of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, April, 1939, I pointed out certain discrepancies in definition and in reported facts which have appeared in the literature. I believe, and so did my associates who knew my work, that I had explained these discrepancies and pointed out a way to avoid them. My work was carefully planned and executed; the pathology has been checked repeatedly by outstanding pathologists and the conclusions verified. My purpose was to clarify and to contribute at least some new knowledge, not to tear down or contradict.

WALLACE E. HERRELL, M.D.

The Mayo Clinic
Rochester, Minnesota
April 18, 1939

tioner—17 specialists rolled into one, as I heard the general man described by one of our number in answer to an attorney's question concerning the difference between him and a specialist.

Fraternally and sincerely yours,

FERDINAND J. SMITH, M.D.

The writer of this letter, Dr. Ferdinand J. Smith, was born in Chicago, February 27, 1862. In 1883, he received the B.S. degree from the Iowa State College (Ames), and the following year, 1883-84, was Instructor at the Massachusetts Institute of Technology. During 1884, he also spent some time in Germany and was made a member of the Deutsche Medizinische Gesellschaft in Berlin. From 1884 to 1887 he attended the College of Medicine, State University of Iowa, and was graduated in March, 1887, with the M.D. degree.

Immediately after graduation, he settled in Alton, Iowa, where he did general practice until 1904, when he went to Des Moines as Dean of the Junior College of Medicine and Head of the Department of Biological Chemistry at Drake University, after having spent some months at Heidelberg in Kossel's laboratory. In 1909, he was made Dean of Men at the University, a position which he held until 1913, when the Drake Medical Department was discontinued. During his early years as a practitioner, Dr. Smith was surgeon to the C. & N. W. R. R. (1887) and to the C. M. St. P. and Omaha R. R. (1889).

Upon leaving Des Moines in 1913, he resumed the practice of medicine at Little Rock, Iowa, where he remained until his retirement. During this interval he was active in medical society work and helped to organize the Northwest Iowa Medical Association. From 1918 to 1919 he served as coroner for Lyon County and at one time was Bacteriologist to the Auxiliary State Health Laboratory for Northwest Iowa. As late as 1937, he was President of the Dickinson County Interprofessional Association. In spite of a heavy professional burden, Dr. Smith prepared many papers on medical subjects. Within the last few years he published "The Transition from Franklin Medical School to the Keokuk College of Medicine of the State University of Iowa," an interesting treatise dealing with the early history of medical education in the state.

To the Editor:

In the paper by Herrell on "Studies on the Endometrium in Association with the Normal Menstrual Cycle, with Ovarian Dysfunctions and Cancer of the Uterus," published in the April number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, the author takes issue with a number of authors, including Novak and Yui, that hyperplasia of the endometrium is often found in association with adenocarcinoma of the uterus, and then presents very impressive evidence from his own series of cases that such an association is exceedingly common. He prefers, however, to apply to the Swiss-cheese pattern of proliferative endometrium the designation of "proliferative type of endometrium with cystic change." He does not, in quoting our paper, explain that we particularly emphasized that only the postmenopausal type of hyperplasia was considered important from this standpoint, and that we took great pains to discuss the frequent misapplication of the term hyperplasia, which, however, is so firmly entrenched in the literature that no one individual's fiat will dislodge it.

"The term hyperplasia, therefore, as we have many times stressed, is a rather loose and not an altogether satisfactory one; but it is now so well established that it would not be easy to dislodge it. The proper evaluation of the histologic variations of hyperplasia can be made only if one bears in mind that they represent merely the reaction of the endometrium to varying degrees of estrin stimulation, and that there is an insensible gradation from the normal proliferative or interval type of endometrium to the so-called mild hyperplasia than to the hyperplasia of frank

Items

American Congress On Obstetrics and Gynecology

The attention of the readers of the JOURNAL is called to the American Congress on Obstetrics and Gynecology, which is scheduled to meet in Cleveland, Ohio, on September 11-15, 1939.

Applications for membership should be addressed to the Headquarters, 650 Rush Street, Chicago, Ill.

Pacific Coast Society of Obstetrics and Gynecology

The next meeting of the Pacific Coast Society of Obstetrics and Gynecology will be held in Portland, Oregon, October 4 to 7, 1939. For further information apply to T. Floyd Bell, Secretary-Treasurer, 400 Twenty-Ninth St., Oakland, Calif.

Third All India Obstetric and Gynaecological Congress

The Third All India Obstetric and Gynaecological Congress will be held in Calcutta in December, 1939. The principal subjects of discussion will be: Anemia of pregnancy, functional uterine hemorrhage, and maternity and child welfare. The Provisional Scientific Committee has formulated a scheme to facilitate investigations on those subjects. The Secretary will be at the service of any investigator to supply any relevant information. All communications are to be addressed to Dr. S. Mitra, Secretary, Provisional Scientific Committee, 3, Chowringhee Terrace, Calcutta.

Poliomyelitis Associated with Pregnancy

Under a grant from the National Foundation for Infantile Paralysis, an investigation is being conducted at the Hospital for Joint Diseases in New York City of the obstetric difficulties in patients who have had infantile paralysis. The assistance of physicians who have encountered such cases is asked by those in charge of this research, Dr. Samuel Kleinberg and Dr. M. T. Horwitz, who may be addressed for questionnaire blanks and further information, at the Hospital for Joint Diseases, Madison Avenue and 123rd Street, New York City.

Books Received

A TEXTBOOK OF NEURO-RADIOLOGY. By Cecil P. G. Wakely, Fellow of King's College, London; Senior Surgeon, King's College Hospital, London, etc., and Alexander Orley, Fellow of British Association of Radiologists; Radiologist of West End Hospital for Nervous Diseases, etc. Illustrated, 336 pages. Williams & Wilkins Co., Baltimore, 1939.

PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY. Volume II. By H. B. Van Dyke, Head of Division of Pharmacology, Squibb's Institute for Medical Research, etc. Illustrated, 402 pages. University of Chicago Press, Chicago, 1939.

PHYSIOLOGY OF THE UTERUS. With Clinical Correlations. By Samuel R. M. Reynolds, Fellow, John Simon Guggenheim Memorial Foundation, University of Rochester School of Medicine and Dentistry, Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. Illustrated, 447 pages. Paul B. Hoeber, Inc., New York, 1939.

THE VAGINAL DIAPHRAGM. By Dr. Le Mon Clark, Chicago. Illustrated, 107 pages. The C. V. Mosby Co., St. Louis, 1939.

LEHRBUCH DER FRAUENHEILKUNDE, in zwei Baenden. Von Professor Dr. W. Weibel, Vorstand der II. Universitaets-Frauenklinik in Wien. Zweiter Band: Gynaekologie. Mit 531 zum Teile mehrfarbigen Abbildungen im Text mit 16 farbigen Tafeln, 398 Seiten. Urban & Schwarzenberg, Berlin-Wien, 1939.

L'OBSTÉTRIQUE A TRAVERS LES AGES. Par L. Devraigne, Accoucheur de Lariboisière, etc. Avec 77 figures dans le texte, 138 pages. Gaston Doin & Cie, Paris, 1939.

PROBLEMS OF AGEING. Biological and Medical Aspects. Edited by E. V. Cowdry, Washington University in St. Louis. 121 illustrations, 758 pages. Williams & Wilkins Company, Baltimore, 1939.

FEMININE HYGIENE IN MARRIAGE. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

SUPERFLUOUS HAIR AND ITS REMOVAL. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

LEHRBUCH DER GEBURTSHILFE. Herausgegeben von Professor Dr. W. Stoeckel, Universitaets-Frauenklinik in Berlin. Fuenfte, verbesserte Auflage, mit 639 zum grossen Teile farbigen Abbildungen im Text, 1054 Seiten. Verlag von Gustav Fischer, Jena, 1938.

operation for arrest of labor. Child 3,154 gm., lived two hours. Comment: Operative procedure probably the primary factor in fetal death. Patient of the dystocia dystrophic type.

CASE 10.—No. A44225. Aged 21 years, small brachypellic type pelvis, 10.0-12.0 cm. Version and extraction for arrest of labor after twenty-two hours. Child 4,059 gm., stillborn. Delay in delivering aftercoming head cause of fetal death. Comment: The size of the child should have been recognized and cervical cesarean section performed.

SUMMARY

A total of ten fetal deaths in this series gives a gross fetal mortality of 1.66 per cent for the series. As far as obstetric procedures at the time of labor are concerned, the first five cases showing fetal abnormalities and antepartum death should be eliminated, giving a corrected fetal mortality of 0.82 per cent.

GENERAL CONCLUSIONS

As I have previously pointed out, it appears from this and other studies that we must reconstruct our views with regard to the architecture of the female pelvis. The incidence of the brachypellic type in but one-third of the series makes it appear that this type does not represent the norm in the adult white women of our population. Studies now under way in our clinic on a group of prepubescent girls have shown this type of pelvis to be relatively infrequent. It is our present opinion that environmental influences, especially in early life and during puberty, may be of some significance in determining the configuration of the adult pelvis. In the platypellic group in this series certain sacral changes suggest that rickets probably plays a major rôle as an etiologic factor.

That the dolichopellic and mesatipellic types appear to facilitate spontaneous delivery is further evidenced by the incidence of cesarean section in these two groups, 0.0 per cent and 0.7 per cent, respectively, while in the brachypellic and platypellic types the incidence is 4.3 per cent and 15.4 per cent, respectively. The incidence of operative intervention of all kinds in the series shows the same trend.

The routine use of simple, inexpensive roentgen methods, especially in primiparous women at term, possesses many advantages. Not the least of these is the knowledge we are bound to gain in the treatment of cases of real and suspected disproportion. The use of the lateral roentgenogram during the test of labor makes for scientific accuracy.

Finally, if we are to continue our attack on the problems of maternal and fetal mortality an important objective must be better obstetric care at the time of labor. By making available to the obstetrician exact knowledge of pelvic dimensions we will further reduce the incidence of hit or miss methods in obstetric procedure.

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UTEROSALPINGOGRAPHY WITH SKIODAN ACACIA

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A DEFINITE step forward in gynecologic diagnosis was made by Heuser of Buenos Aires when, in 1921, he made the first injection of iodized oil into the uterus, through the cervix, and thus demonstrated that x-ray studies following this procedure visualized the uterine cavity and the Fallopian tubes. It has now become possible to photograph the normal contour of the uterus and tubes and recognize changes from the normal as to size, position and irregularities of the uterus, and patency or stenosis of the tubes.

Numerous other workers in this field now known as uterosalpingography have added to our knowledge.

Until very recently, iodized oil was the only suitable radio-opaque substance that gave satisfactory results in uterosalpingography. Iodized oil is far from an ideal medium. Reports are continually being published, describing such undesirable and unexpected complications as salpingitis, jaundice, chills and fever, pelvic abscesses, encapsulated oil and foreign body formation in the culdesac and entrance of lipiodal into ovarian and other veins. This has given just cause for hesitation in using iodized oil in uterosalpingography, and has intensified the search for a nonirritating and easily absorbed, nontoxic, radio-opaque liquid, whose use will not be complicated by any untoward results.

Following the report last year of Titus, Tafel, McClellan and Messer on skiodan-acacia (Winthrop), we felt that such a solution should be worth investigating, and if found satisfactory, we would eliminate the disadvantages encountered with the use of iodized oil. We, therefore, present this series of 24 cases in which skiodan-acacia solution was used with the technique that we have developed, and which we feel gives satisfactory pictures and results.

Sodium mono-iodomethane sulphonate (skiodan) in watery solution is entirely nonirritating and noncaustic and has been used extensively, both intravenously and by the retrograde method in urology. It has, however, insufficient viscosity for uterosalpingography. Many combinations with viscid media were attempted to reproduce the viscosity of lipiodal. Skiodan mixtures with starch, dextrose, glycerin, and tragacanth were attempted and rejected as unsuitable. Acacia was finally used and after much animal experimentation with concentrations of acacia from 10 to 40 per cent and skiodan from 10 to 40 per cent in water, saline and dextrose, it was found that aqueous skiodan 40 per cent in 20 per cent acacia was the maximum specific gravity suitable for tubal visualization together with the minimum of

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local irritant reaction. Microscopic examination of rabbit uteri, tubes, and peritoneal tissue reveals that the above mixture produces an insignificant inflammatory reaction that has completely healed after twenty-four hours.

This accumulated experience has led to the acceptance of certain basic facts. As a result of all this the following rules should be understood and adhered to in the performance of uterosalpingography:

1. All preliminary gynecologic studies should be completed before uterosalpingography is attempted.

2. This procedure should be done about a week after the patient finishes her menstrual period; as at this time the uterus and tubes are in a quiescent state, and less subject to spasmodic contractions. At this time there is little danger of disturbing a possible early pregnancy.

3. The procedure must not be done in the presence of: (a) an acute or subacute infection of the genital tract, real or suspected; (b) bloody or purulent cervical discharge; (c) temperature, due to any cause.

4. Qualities of the radio-opaque medium: (a) The radio-opaque fluid must be liquid enough for easy injection and yet sufficiently viscid not to escape too quickly after being injected. (b) The fluid must not cause injury nor irritation to the patient's tissues. (c) The fluid must not cause excessive discomfort, pain, or untoward reaction. (d) The fluid should be easily and quickly absorbed into the circulation, and when so absorbed, cause no toxic symptoms or reaction. (e) The radiograph must be clear and brilliant enough to make interpretation of the gynecologic pathology satisfactory.

5. When the x-rays are studied, it must be remembered that the lumen of the tubes does not become distended if the outer end is open, for this permits leakage of the opaque medium into the peritoneal cavity. If the tubes are closed, the solution fills the uterotubal cavity proximal to the point of block and usually gives a clear-cut rounded outline. Abnormalities in the uterine cavity are marked by differences from the normal triangular-shaped uterine cavity.

The test is not meant to supplant the Rubin test (gas insufflation) but to supplement it and thus add additional information.

After some experimentation and modification, the following is the technique that we found to be most satisfactory with this skiodan-acacia solution.

TECHNIQUE

Hospitalization is not required, and no anesthesia is needed. Very nervous or apprehensive patients may be given morphine sulphate gr. 1/6 before starting. The patient voids just before the procedure is carried out.

Instruments used are: vaginal speculum, cervical tenaculum, uterine sound, 20 c.c. Luer syringe, and a uterine cannula that fits the syringe and has a rubber guard that prevents escape of the fluid through the cervix.

The patient is placed in the lithotomy position on a genitourinary roentgen table. The vulva is scrubbed with soap and water and flushed with sterile water; the vaginal speculum is inserted, and the cervix is grasped with the tenaculum and pulled down. The cervix and vagina are swabbed with an aqueous antiseptic. The uterine sound is inserted to determine the depth and direction of the uterus, and also to make the entrance of the uterine cannula easier. The uterine cannula is inserted for a distance of 2 or 3 cm. up to the rubber guard, making a tight fit. The speculum may be left in situ but is better withdrawn. The skiodan-acacia solution, warmed to room temperature, is withdrawn into the 20 c.c. syringe and injected into the uterine cavity through the uterine cannula with slow, gentle, steady

TABLE I. REPORT OF CASES

	AGE	CLINICAL DIAGNOSIS	X-RAY FINDINGS
1	24	Normal post partum	Normal uterus; tubes patent
2	28	Normal post partum	Normal uterus; tubes patent
3	26	Normal post partum	Normal uterus; tubes patent
4	36	Normal post partum	Normal uterus; tubes patent
5	26	Normal post partum	Normal uterus; tubes patent
6	28	Normal post partum	Normal uterus; tubes patent
7	35	Left tubo-ovarian mass	Both tubes distended; closed
8	47	Fibroid uterus (submucous)	Normal uterus; tubes patent
9	34	Postoperative salpingectomy	Normal uterus; tubes closed
10	24	Postpuerperal parametritis	Normal uterus; tubes closed
11	26	Chronic pelvic inflammatory disease	Normal uterus; tubes closed
12	31	Primary sterility	Normal uterus; tubes closed
13	36	Fibroid uterus	Large uterus; right tube closed
14	29	Secondary sterility	Normal uterus; tubes closed
15	26	Right oophorectomy, left salpingectomy	Normal uterus; proximal 2 cm. right tube open
16	36	Secondary sterility	Normal uterus; right tube long and narrow; left tube closed
17	24	Left ectopic pregnancy	Normal uterus; right tube patent Proximal 2 cm. of left tube patent
18	35	Bilateral tubo-ovarian disease	Normal uterus; tubes closed
19	35	Right ovarian cyst	Normal uterus; long narrow right tube; normal left tube
20	31	Fibroid uterus	Normal uterus; tubes patent
21	32	Right oophorectomy	Normal uterus; left tube patent Proximal 1 cm. right tube patent
22	36	? Fibroid uterus	Incomplete filling of uterus; tubes closed
23	16	Left ovarian cyst	Normal uterus; long narrow left tube; right tube patent
24	22	Pelvic endometriosis	Normal uterus; tubes patent

SUMMARY AND CONCLUSIONS

1. Twenty-four* cases are presented where radio-opaque aqueous solution of skiodan-acacia (Winthrop) was used for uterosalpingography.

2. In none of the 24 cases were there any untoward results or complications.

3. All cases showed complete absorption of the solution within thirty to fifty minutes.

4. The roentgenograms obtained were sufficiently clear for satisfactory interpretation.

5. Refinement in x-ray technique should give even clearer shadows.

6. This new radio-opaque aqueous solution of skiodan-acacia is recommended for further study as to its use in uterosalpingography.

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*Four cases are from the Gynecological Service of Dr. Edward Davin at the Lincoln Hospital.

pressure. It has been noted that when 5 or 6 c.c. of the solution has been introduced, the patient will complain of some suprapubic cramplike pains; after several seconds, an attempt is made to gently inject some more solution, and as soon as a definite resistance is felt to the plunger, it may be assumed that the uterine cavity and tubes are well filled. At this point, the first x-ray exposure is made; following this picture, and after waiting for three minutes, it will be found that another 5 c.c. of the solution can be injected, and five minutes after the first film was taken, a second picture is made.

All patients complained of more severe cramps when the skiodan was apparently entering the peritoneal cavity, but this pain was never extreme, nor did it last long. Experience will soon teach one the right amount of pressure to use to obtain the optimum result, without causing injury to closed tubes. It is obvious that the second x-ray picture is invaluable in confirming tubal patency, tubal pathology, or extratubal masses.

After the second film is taken, the syringe and cannula are withdrawn. Some of the skiodan will leak back into the vagina, but enough is retained to give several additional pictures.

Pictures taken thirty to fifty minutes after the injection of the solution show that all of it has already been absorbed and none remains in the peritoneal cavity to become encapsulated or cause further peritoneal irritation.

We present 24 cases selected at random but within the rules mentioned above.

The first six cases may be considered normal controls and in these the uteri were normal in contour, the tubes were patent, and the solution was absorbed rapidly, and no evidence of toxic action was noted.

Cases 10, 11, and 18 were patients with quiescent pelvic inflammatory disease. There was no flare-up of the infection following the use of the skiodan solution. The films showed closed tubes, normal uteri, and the medium was equally rapidly absorbed.

In Cases 16 to 19, we were fortunate in having lipiodal x-ray pictures to compare with the ones we took. Although the lipiodal pictures are somewhat more brilliant, it may be seen that the skiodan shadows are intense enough for an adequate interpretation. Improvement of the x-ray technique with skiodan will help to improve the intensity of the skiodan shadows.

We had hoped, in doing uterosalpingograms with the skiodan solution, that the kidneys might be visualized at the same time. Although several of the pictures suggest a somewhat better visualization of the kidneys than the ordinary flat plate, we must, however, confess our disappointment in the use of skiodan for this purpose, and feel that in these amounts and by this method there is insufficient concentration of the skiodan in the genitourinary tract to give worthwhile shadows.

Patient in Case 20 complained of a slight transient urticaria developing several hours after the injection.

Patient in Case 7 complained of a mild general itch, which also lasted for several hours after the injection.

Both of these manifestations might have been due to sensitivity to acacia.

In the entire group, representing a wide variety of gynecologic conditions, we have experienced no complications of serious import. We feel justified on the basis of our satisfactory results, in recommending the use of skiodan-acacia solution for uterosalpingography with the technique described above for further study and experiment.

TABLE I. INDICATIONS FOR STERILIZATION

NO. OF CASES	INDICATION
9	Hypertensive vascular disease
7	Repeated cesarean sections
4	Pulmonary tuberculosis
2	Myomata uteri
1	Pott's disease
1	Acute nephrosis
1	Pyelonephritis
1	Rheumatic heart disease
1	Placenta previa (in a grand multipara)
1	Intrapartum infection (with cephalopelvic disproportion)
14	Psychiatric:
	8 Feeble-mindedness
	4 Jacksonian epilepsy with progressive mental deterioration
	1 Imbecility
	1 Manic depressive psychosis
42	

Following the operation, after periods which varied between 1.6 and 8.0 years, the patients were interviewed in regard to the occurrence of menopausal symptoms. The average interval between the hysterectomy and the interview was 4.1 years. Of the 42 patients, 13, or 30.8 per cent, were followed five years or more; 34, or 80.9 per cent, were followed three years or more; while 41, or 97.6 per cent, were followed two years or more. As shown by Sessums and Murphy, if a patient is going to develop menopausal symptoms after hysterectomy, these become manifest within the first two years in over 90 per cent of cases and within three years in 95 per cent. Each patient was questioned in person in regard to the various signs and symptoms of the menopause, including hot and cold flushes, sweating, headache and vertigo, libido, indigestion, psychic and nervous disturbances, and weight gain. However, with the exception of hot flushes the symptoms were often so vague that it seemed best to evaluate the cases on the basis of hot flushes only. The term, menopausal symptoms, in this paper therefore, refers only to hot flushes. Sessums and Murphy used the same criterion.

TABLE II. THE INCIDENCE OF PHYSIOLOGICAL MENOPAUSE DEVELOPING IN WOMEN UNDER FORTY COMPARED WITH THE INCIDENCE OF SURGICAL MENOPAUSE FOLLOWING HYSTERECTOMY WITH OVARIAN CONSERVATION

CONDITION	SOURCE	NUMBER OF CASES	PERCENTAGE DEVELOPING SYMPTOMS
Hysterectomy done on normal pregnant and puerperal women before the age of 36 with symptoms developing before the age of 40	Present series	42	16.6
Physiologic menopause	Norris	200	1.5
	Novak	100	3.0
	Sanes	567	7.77
Hysterectomy done on women menstruating regularly but irrespective of age	Mandel and Bürger	96	67.7
	Peterson	27	74.0
	Graves	26	81.0
Hysterectomy done before the age of 37	Kretzschmar and Gardiner	64	57.8
Hysterectomy done before the age of 36 with symptoms appearing before 40	Sessums and Murphy	91	43.9

THE ROLE OF HYSTERECTOMY IN THE PRODUCTION OF MENOPAUSAL SYMPTOMS

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THE influence of hysterectomy in the production of menopausal symptoms, even when both ovaries are conserved, remains an open question. The many animal experiments dealing with this problem are scarcely applicable to the human being because of differences in anatomic relationships.[1, 2] The studies which have hitherto been reported on the effect of hysterectomy in women are similarly inconclusive because of the associated pelvic pathology.[3-11] In the presence of fibromyomas or pelvic inflammatory disease, for which most of these hysterectomies were done, injury to the ovarian blood supply is a distinct likelihood and if, in such cases, menopausal symptoms later develop it is difficult to know whether they are attributable to the absence of the uterus per se or to an inadequate blood supply to the ovaries. In some of the reported cases, furthermore, the patients were so near the usual age of menopause as to invalidate conclusions. We report the present small series of 42 hysterectomies because they were done, almost without exception, on women who had no demonstrable pelvic pathology and who were still in their reproductive prime. The operations were performed for the sole purpose of sterilization, it being a common practice in this Clinic several years ago to carry out sterilization, when indicated, by means of hysterectomy provided the patient did not wish menstruation to continue. The indications for sterilization in the series are shown in Table I. In order to obviate the age factor, no patient was included in the study who was over 35 at the time of operation, the average age being 29 years. The parity distribution was primiparas 5, secundiparas 6, and other multiparas 31. Twenty-five of the patients were white and 17 colored.

With four exceptions the operations were carried out on patients who were, or had recently been, pregnant. Thus, in 15 cases the hysterectomy was performed immediately after cesarean section; in 16 instances it was done in early pregnancy on the unopened uterus, while in 7 cases, it was carried out one to six weeks after delivery. When done on such pregnant or puerperal uteri, hysterectomy would seem to impose a minimal likelihood of injuring the ovarian blood supply, since the physiologic elongation of the ovarian and infundibulopelvic ligaments makes it possible to clamp, ligate, and sever these structures without encroaching upon the immediate neighborhood of the ovaries. The 42 hysterectomies were done by a number of operators. With the exception of one panhysterectomy, the operations were all supravaginal hysterectomies, but no particular effort was made to leave endometrial tissue. In 36 cases both ovaries were left in situ, but in 6, one ovary was removed along with the uterus.

ENDOMETRIOSIS IN LAPAROTOMY SCARS

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ALTHOUGH endometriosis in laparotomy scars may no longer be considered rare, the condition is seen infrequently enough to warrant reports of new cases. It was these nodules in a scar following cesarean section which helped form the basis of Sampson's theory of transtubal implantation, which has had such widespread influence in stimulating interest in the general subject of endometriosis.

In 1920 Mahle and MacCarty[2] reported 2 cases, following ventral suspension of the uterus and shortening of the round ligaments, respectively. They were unable to demonstrate a direct fistulous communication between the uterus and abdominal wall, nor were Nicholson[3] or Lemon and Mahle,[4] in their respective reports of 32 and 9 cases. Heaney[5] cites 29 cases in 1925, adding 2 of his own, while Danforth[6] reported an additional case at the same time. In 1928 Mason and Simon[7] reported 16 cases in a paper on uterine fistula and suggested the injection of radio-opaque media as an aid in diagnosis, the injection of methylene blue also being suggested at a later date by Keene and Kimbrough.[8] The same year, Ballin[9] collected 40 cases which he considered as direct communications between the uterus and tubes and abdominal wall. Many other cases have been reported recently.[10-12]

The type of operation preceding these lesions varies considerably, but operations upon the tubes, round ligaments, ventral suspensions, and cesarean sections head the list, although the operation may be extrapelvic, as demonstrated by a recent case[13] of endometriosis in the scar following operation for a strangulated inguinal hernia and several cases following appendectomies.[1, 7]

M. H., colored, aged 37 years, was admitted to the University Hospital June 6, 1937, with the chief complaint of pain and bleeding in an abdominal scar. Twenty years previously she had had an appendectomy and bilateral salpingectomy for acute appendicitis and acute salpingitis. The past history and family history were nonessential. The general history was negative except for bleeding from the rectum during the present illness. There was no hematuria. Her menses were of the 13-28-4 variety. Leucorrhea had been present for twenty years. The last menstrual period was May 18, 1937, the previous menstrual period was April 16, 1937.

The present illness began in 1935, or eighteen years after the original operation, with pain in the incision and right lower quadrant during the catamenia, beginning one week before its onset and lasting three to seven days after. In May, 1937 a small nodule was noticed in the incision which bled a little each day, but more profusely during menstruation.

The general examination showed a poorly developed colored woman. The breasts were normal. The abdomen showed a low midline scar with a small, indurated area in the middle which bled easily. The vulva, vagina, and cervix were essentially normal. There was no induration of the rectovaginal septum. The uterus was small, attached to the abdominal wall and fixed. There was a firm, smooth mass about 6 cm. in diameter in the left adnexal region which moved with the uterus.

Proctoscopic and cystoscopic examinations unfortunately were not made. The urine was negative. The Kolmer and Kahn tests were positive. R.B.C., 3,610,000; Hb., 65 per cent; W.B.C., 6,850.

On June 9, 1937, under gas-oxygen-ether anesthesia, a laparotomy was performed; incision was made to include the old scar. Near the middle of the incision, above the fascia, a blood-filled cyst was encountered. The right uterine cornu and right ovary were densely adherent to the peritoneal scar, a pedunculated uterine myoma was found arising on the left. A supravaginal hysterectomy and bilateral oophorectomy were performed.

The results of the present study may be seen in Table II, together with figures culled from the literature, showing (a) the incidence of menopausal symptoms developing in women under forty who have not been subjected to operation and (b) the incidence of menopausal symptoms following hysterectomy with ovarian conservation.

It is apparent that the incidence of menopausal symptoms in our series, namely, 16.6 per cent, was decidedly less than that hitherto reported in the literature, that is, 43.9 to 81.0 per cent. In other words, when hysterectomy is performed on the pregnant or the puerperal uterus in the absence of pelvic pathology, it is much less likely to produce menopausal sequelae than when done in the presence of fibromyomas and pelvic inflammatory disease. While this circumstance may be subject to several interpretations, it would seem most plausibly explained by the greater technical difficulties of hysterectomy in the presence of pelvic pathology and the greater likelihood of injuring the ovarian blood supply. If this fact be true, it suggests that hysterectomy with ovarian conservation brings about menopausal symptoms through injuring the ovarian blood supply rather than through the absence of the uterus per se.

The writer wishes to acknowledge the assistance given by Dr. Marion Fairfield, now of Nashua, New Hampshire, in interviewing the patients.

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Simpson, S. Levy, and Von, Cecil A.: Feminization in a Male Adult With Carcinoma of the Adrenal Cortex, Endocrinology 22: 604, 1938.

A case of feminization of a male aged 34 is described, together with the partial remission of symptoms following removal of an adrenal carcinoma. Death subsequently followed the recurrence of growth and metastases. The patient excreted a considerable excess of estrogenic hormone (probably estrone), which disappeared after operation and returned with the recurrence of the growth. The histologic picture showed certain differences from that of an adrenal carcinoma removed from a virile woman, who secreted an excess of comb-growth hormone. The histologic differences may explain why, in the one case, estrogenic hormone and, in the other case, comb-growth hormone were excreted. The clinical and biologic evidence suggests that the adrenal tumor was directly or indirectly responsible for the excess of estrogenic hormone found in this case of feminization. A similar hypothesis was advanced in a previous paper for the presence of an excess of comb-growth hormone in the urine of virile women.

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ENDOMETRIAL PATTERNS IN DYSMENORRHEA

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IN A RECENT paper[1] we have presented the findings in a series of cases of functional dysmenorrhea which demonstrated that a large percentage of such cases had a high blood and urine level of the follicular hormone throughout the menstrual cycle. We had at that time no clinical method of determining the quality or physiologic activity of the luteal hormone. But, from the concept of the interrelationship of the two hormones, it seemed probable that such high levels of the follicular hormone would be accompanied by deficiencies of the luteal hormone, and that since theelin increases uterine contractions, the presence of excessive or unbalanced quantities of this substance might account for the pain incident to menstruation.

The introduction of the endometrial biopsy has given us a method by which the physiologic activity of the corpus luteum may be judged. From cases so studied we wish to present the findings in 50 cases of functional dysmenorrhea.

The cases selected for study were those whose main, but not necessarily only complaint, was dysmenorrhea and in whom there were no gross systemic or pelvic abnormalities. The study of each case included a general and pelvic examination, blood count, urinalysis, Kahn, basal metabolic rate, premenstrual blood hormone determinations according to the Frank-Goldberger technique, and premenstrual endometrial biopsies.

There is no universally accepted classification of the endometrial changes during a menstrual cycle. Sturgis and Meigs[2] have classified the cyclic changes as consisting of two phases, the proliferative and the secretory, corresponding to the periods of function of the Graafian follicle and the corpus luteum, respectively.

Herrell and Broders[3] have used the terms proliferative and differentiative to apply to the same phases. They have further called attention to the fact that in some cases of menstrual abnormalities, the endometrium does not complete its cycle of growth and differentiation, which results in persistent phases of the cycle and that such endometrial patterns indicate the type and degree of ovarian failure. Randall and Herrell[4] have further pointed out that besides the types of endometria in which arrest of the development is the only finding significant of ovarian failure, there may also be cystic changes in the endometrium as the result of an abnormality of hormone balance in either phase. They also point out that the idea that the corpus luteum functions in an "all or none" manner is erroneous. Glandular cystic hyperplasia in a secretory endometrium indicates that ovulaton may have occurred but that a normally functioning corpus luteum has not followed.

The findings in the endometrial biopsies in the cases studied fell into the following groups: Normal secretory or differentiative reactions, 18 cases; secretory or differentiative with cystic changes, 9 cases; per-

Pathologic examination showed no true fistula. The scar (Fig. 1) contained numerous areas of endometriosis. The right ovary and myometrium showed an occasional endometrial gland.

The postoperative course was uneventful and the follow-up has shown the patient to be in good condition with no complaints.

The objective and subjective symptoms of this case are typical, as are the operative and pathologic findings. For these cases the operative morbidity and mortality rates are very low, the results excellent, often ovarian conservation being possible. The long latent period in this and other cases is difficult to correlate with Sampson's theorem, for it seems unlikely that transplanted endometrium could remain dormant

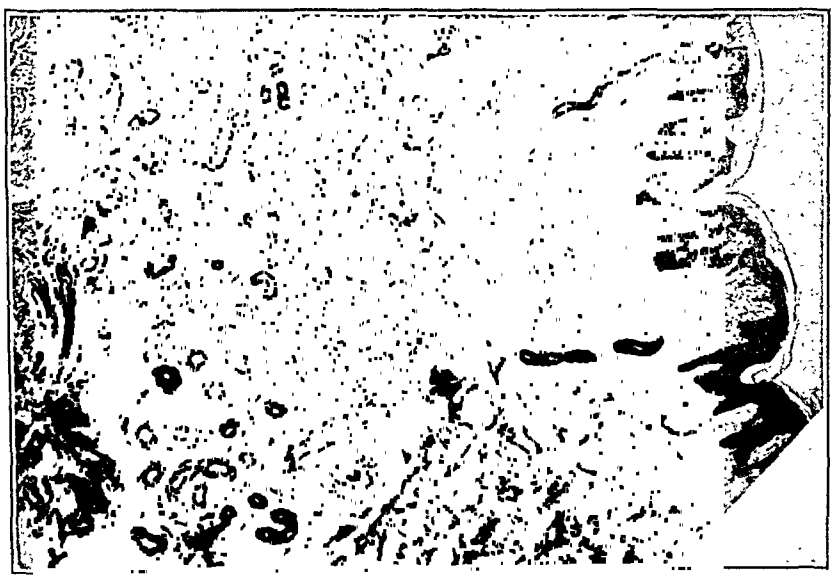


Fig. 1.—Section of abdominal scar showing numerous endometrial glands.

for a period of twenty years, suddenly springing into activity. One is forced to admit that, despite the large amount of work devoted to this subject, we have not yet arrived at a theory which explains every case of endometriosis.

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Sulfanilamide given to pregnant women shortly before or during labor is absorbed in the gastrointestinal tract and passes readily through the placenta to the fetus to appear in almost equal concentrations in maternal and fetal venous bloods.

Hugo Ehrenfest.

Anemia was a common but significant finding in all of the cases. There was a tendency for the basal metabolic rate to be low, 15 being below minus 10, 30 within normal limits, and 5 above plus 10. It is interesting to note that the group in which the basal rate was consistently low was that in which there was a cystic secretory phase of the endometrium. Urinalyses were negative in all cases as were the Kahn tests. Associated menstrual abnormalities were present in 15 cases with a tendency for these to occur when the endometrium was of an abnormal type.

In seeking to determine the endocrine status on the basis of the endometrial picture, we interpret that of the 50 cases of functional dysmenorrhea, there were 27 in which ovulation had occurred but in only 18 of these was ovulation followed by normal corpus luteum



Fig. 2.—Cystic proliferative (follicular) phase. A married woman, aged 28, whose chief complaints were dysmenorrhea and hypomenorrhea and sterility. Biopsy taken twenty-seven days after onset of preceding period and menstruation followed six days later, lasting seven days. Premenstrual blood estrogenic substance positive, gonadotropic negative, basal metabolic rate minus 13.

function. All of these 27 apparently had adequate and 9, excessive follicular activity. Twenty-three of the 50 apparently had no corpus luteum at all; but of these, 21 had follicular function and 11 in excessive amounts. It seems probable, therefore, that in 18 there was a normal balance between the follicular-corpus luteum function and in 30 there was follicular function present but unbalanced by corpus luteum function. In only 2 cases was there a deficiency of both functions.

The endometrial biopsy gives a more accurate estimation of the physiologic activity of the ovarian hormones than bio-assay of the blood and urine for the hormone content, because the endometrium reflects the extent to which the hormones are physiologically effective, whereas

sistent late proliferative phase, 10 cases; persistent early proliferative phase, 2 cases; proliferative cystic hyperplasia, 11 cases.

In the cases with normal secretory function, eleven had no other complaints, one had polymenorrhea, and three oligomenorrhea. The basal metabolic rate was within normal limits in all except four cases. The outstanding finding in this group was the occurrence of pelvic congestion in 10 cases. In all cases but two there was at least a normal amount of the estrogenic hormone in the blood premenstrually.

Secretory or differentiative changes with cystic hyperplasia occurred in 9 cases. Of these, there was one case each of oligomenorrhea and polymenorrhea. The uterus was infantile in type in 3 cases and retroverted with pelvic congestion in 1. The basal metabolic rates were below normal in all except 2 which were within normal limits. Estro-



Fig. 1.—Persistent proliferative (follicular) phase. A married woman aged 30 years, whose chief complaint was severe dysmenorrhea with prolonged flow and clots since resection of both ovaries seven years ago. Biopsy taken twenty-seven days after onset of previous period and menstruation followed one day later, lasting twenty days. Premenstrual blood hormone tests: Very strong positive estrogenic (Frank-Goldberger technique), reaction I gonadotropic (Zondek technique), basal metabolic rate minus 12.

genic substance was demonstrable in all except 3. Gonadotropic substance was present in only 1 case.

Arrest of the endometrium in the proliferative phase occurred in 23 cases in 11 of which cystic hyperplasia was also present. Estrogenic substance was demonstrable in 14 cases and absent in 9, 2 of the latter group having positive gonadotropic hormone tests. The uterus was normal in all cases except one which was infantile in type and one retroverted. There were 3 cases of pelvic congestion. The basal metabolic rate was practically normal in all cases. This group included 4 cases of polymenorrhea, 4 of oligomenorrhea, and 2 of mammary hyperplasia.

titration merely gives an estimate of the amount present at a given time and tells nothing of how efficient it is in the organism. It must be remembered, however, that there are occasions in which the ovary may be normal in function but the uterus unresponsive.

Menstrual disorders cannot be classified by symptoms. In reviewing this small series of cases we find that each type of abnormality of the menstrual flow may occur with any type of endometrium. Amenorrhea was of course not included. Dysmenorrhea is a symptom and must be treated as such. Each case must be investigated fully if any hope of success is to be realized. To give a patient with negative physical findings hormone therapy on the presumption that there is a glandular dysfunction will lead to negative results in many cases. Pelvic congestion, as demonstrated in this series, is an important factor in the production of many of the gynecologic symptoms. It is usually the result of improper sex hygiene. It apparently was the underlying cause of pain in 13 of the otherwise normal individuals in this series of cases. Even when all factors have been thoroughly investigated there still remains a small group of cases in which no positive findings are present to account for the pain.

SUMMARY

1. Fifty cases of functional dysmenorrhea were studied with especial emphasis placed on the findings from endometrial biopsies.

2. Of the 50 cases, 18, or 36 per cent, had normal endocrine function and 32, or 64 per cent, had some degree of ovarian failure. Of these failures, 30, or 60 per cent, were primarily corpus luteum deficiencies; 20, or 40 per cent, showed associated excessive follicular activity. Only 2, or 4 per cent, showed deficiency of both hormones.

3. Of the cases within normal hormone balance, 10, or 20 per cent, had pelvic congestion present as a possible etiologic factor.

4. In 8, or 16 per cent, there was nothing to account for the dysmenorrhea.

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The author emphasizes that a foreign body in the uterus may produce irritation and inflammatory changes in the uterus and adnexa. Accidents from the use of intrauterine pessaries have been reported from various parts of the world and the author reports an additional one. He comes to the conclusion that the Graefenberg contraceptive ring should be abandoned in favor of safer contraceptive measures.

J. P. Greenhill.

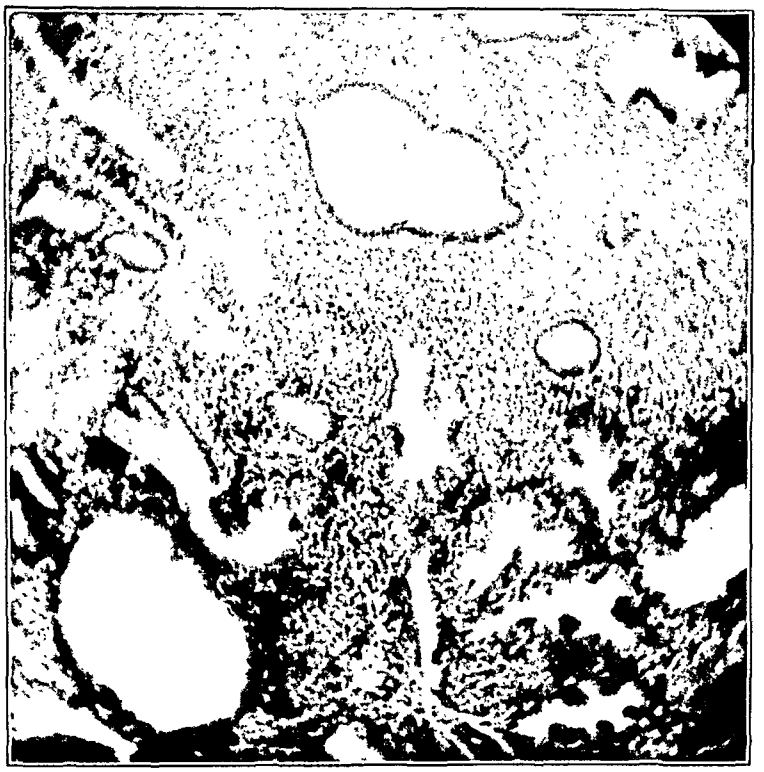


Fig. 3.—Secretory (differentiative) phase with cystic changes. A married woman, aged 25 years, whose only complaint was severe dysmenorrhea since beginning of menstrual function. Biopsy taken twenty-eight days after onset of previous period and menstruation started immediately thereafter. Blood estrogenic substance, strong positive; gonadotropic negative.



Fig. 4.—Secretory (differentiative) phase. An unmarried woman, aged 21, whose only complaint was severe dysmenorrhea. Biopsy taken twenty-four days after previous period and menstruation followed six days later. Blood estrogenic substance, positive, gonadotropic, negative, basal metabolic rate, minus 4.

seventh and eight months. After the fifth month the number of patients showing diminished ureteral response exceeds those showing normal activity. During the last month of pregnancy there seems to be a definite return of muscular irritability as expressed by the measurement of peristalsis and response to stimulation. This diminished peristaltic activity of the ureters seen in pregnancy cannot be explained on the basis of dilatation. On the contrary, dilatation of the ureters during pregnancy is probably in great part dependent upon the atony of the ureters. The etiology of this ureteral atony during pregnancy is, in the opinion of the authors, not due to any mechanical factor but rather has some, as yet unexplained, chemical basis.

Later Traut, McLane and Kuder (1937) pointed out that the characteristics of the ureteral atony are similar in many respects to those affecting the uterine musculature. It was suggested that the phenomena in the two organs may have a similar etiology. The ureteral dilatation is roughly proportional to the degree of atony, and both appear and disappear at similar times with regard to the course of pregnancy. Dilatation and atony appear in the third month and are progressive to the seventh month of pregnancy. During the last two months there is a marked increase in motility, accompanied by a moderate decrease in the dimensions of the tract. Following delivery atony is again marked until the third week, subsequent to which motility returns rapidly to normal levels, which are usually attained during the sixth and seventh weeks post partum. Dilatation of the tract decreases progressively after delivery and reaches practically the normal values at the seventh week of the puerperium.

Hundley, Walton, Hibbitts, Siegel and Brack (1935) felt that the atony of the ureter must be the result of the activity of hormones elaborated during pregnancy. They found hypertrophy of the muscle, edema, and increased vascularity in the whole urinary tract.

Other experiments more closely related to the bladder have been performed by Woolsey and Brooks (1937). They placed cats for long periods in metabolism cages equipped with apparatus for recording continually volume and time of micturition. Micturition volume diminished markedly during estrus or while the animal, female or male, was under the influence of progynon-B. In the female the decrease was correlated with the vaginal smear and estrous cycle. Tremendous increases in micturition volume were observed post partum.

METHODS

The experiments involved considerable technical difficulties. We chose to use rabbits since corpora lutea can be produced in these animals very easily. This animal normally ovulates only at the time of copulation. Injection of antuitrin-S also produces ovulation in the rabbit. Previously the cat has been employed almost exclusively for our studies of vesical function.

Catheterization of the urethra in the rabbit is difficult because the urethral meatus is well up in the vagina. However it was found possible to introduce a fine glass catheter through the urethra into the bladder of the rabbit and make readings of vesical activity after the same manner which has been employed in cats. The animals were always anesthetized with pentobarbital injected intravenously. Before any further procedures were instituted three control readings at ten-day intervals were made to learn the average vesical capacity of the animals. If these readings showed little variation, the experiment was continued.

In this work we used as the criteria of the experiment any changes from the normal vesical capacity which occurred during pregnancy and following ovulation. Records were made of intravesical pressure during filling of the bladder; the pressure remained low until the viscus was reaching the limits of its capacity. The normal vesical capacity of an animal under deep anesthesia is remarkably constant as the readings show. Under pentobarbital anesthesia the vesical muscle does not contract reflexly (Kolb and Langworthy, 1938), and urine escapes only by overflow

THE EFFECT OF PREGNANCY AND THE CORPUS LUTEUM UPON VESICAL MUSCLE*

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THE innervation of vesical muscle has been studied in this laboratory for several years. It became obvious in the course of the experiments that there were factors other than the nervous stimuli to be considered as influencing vesical activity. We early began to exclude pregnant cats from our series of experimental preparations. The bladder appeared to be capable of holding an unusually large volume of fluid at low pressures. This increased capacity was still present for days or weeks after pregnancy was terminated. The conclusion was reached that the vesical muscle was influenced in its capacity not alone by its nerve supply but also by chemical substances carried in the blood.

It has been known for many years that changes in the urinary tract take place with pregnancy. These have been studied particularly in the ureters but have a direct relation to the present experiments. In 1843 Cruveilhier first described dilatation and elongation of the ureter as a frequent accompaniment of the gravid state. He believed that there was a hyperplasia of the tissues composing the walls of the kidney pelvis, the ureter, and the bladder in the form of increased thickness of the muscular and connective tissue elements. In spite of this hypertrophy the lumen of the ureter is dilated. The extent to which these changes appeared varied much in different individuals as well as in the ureters of the same individual, the process usually being more marked on the right side.

Two explanations for these phenomena have arisen. One group has felt that the pressure of the enlarged uterus upon the ureter at the point where it crosses the pelvic brim was the chief factor. However, larger pelvic tumors than those represented by the pregnant uterus were not often productive of the ureteral changes in the nonpregnant patient. Other authors have suggested an atony of the ureteral musculature. Dilatation of the ureter usually reaches its maximum at about the seventh month of pregnancy, and frequently diminishes toward term despite the enlargement and increasing weight of the uterus.

Traut and McLane (1936) studied contraction waves in the ureters of their patients. The normal ureter of the nonpregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded. In the majority of patients this rhythmic activity is definitely changed in pregnancy in varying degrees. The altered peristaltic activity is expressed by diminished amplitude of the peristaltic wave commencing in the third month of pregnancy but reaching its peak during the

*Aided by a grant from the Committee on Scientific Research of the American Medical Association.

TABLE II. EFFECT OF PREGNANCY. CONTROL READINGS

EXP. NO.	1ST CONTROL	10 DAYS LATER	20 DAYS LATER		30 DAYS LATER	40 DAYS LATER	50 DAYS LATER	10 DAYS FOLLOWING DELIVERY
1	22	26	18	Rabbit placed with male.	76			
2	32	28	26		50	56		
3	22	22	24		38			
4	14	26	24		30	40	34	
5	26	28	26		40	40	46	
6	14	14	14		26	56	34	
7	10	16	12		36	36	50	70
8	18	12	16		26	34		
9	28	22	16		36	34	46	60
10	18	14	16		40	32	34	58
11	28	28	32		68	34	58	60
12	24	22	20		54	36	42	66
13	8	4	10		30	24	28	58
14	14	8	12		26	28	22	38
15	22	24	18		50	58		
16	18	16	14		34	24	28	
17	36	22	36		56			

duced by the pressure of the gravid uterus. In other cases the bladder capacity continued to increase through the period of pregnancy.

Following the termination of pregnancy the vesical volume was greater than at any previous period. It appeared that the bladder was free from any pressure from the uterus and could expand to the limits of its capacity. The bladder remained of large volume for three or four weeks following the termination of pregnancy, and it was only at the end of this time that it returned to its normal volume.

C. The final series of experiments had to do with the production of ovulation in the normal rabbit by the injection of antuitrin-S. This group was the most difficult to carry out satisfactorily and the least conclusive. Ovulation did not take place in every case and it was necessary to open the abdomen and make sure of the condition of the ovaries. When ovulation occurred, edema of the vulva and vagina often defeated catheterization. The bladder showed its greatest increase ten days after the injection of antuitrin-S. It may be said that the vesical volume was increased in approximately 50 per cent of the cases. The changes when they did occur were large enough to seem to us significant. They are given in Table III.

TABLE III. PRODUCTION OF OVULATION BY INJECTION OF ANTUITRIN-S IN NORMAL RABBITS

	FIRST CONTROL	SECOND CONTROL 10 DAYS LATER	THIRD CONTROL 20 DAYS LATER		30 DAYS LATER
1	12	12	18	Antuitrin-S	30
2	14	18	16		26
3	18	12	16		34
4	14	14	14		44
5	12	8	14		30
6	14	12	20		28
7	12	14	20		30
8	18	14	12		38
9	8	10	8		24
10	14	20	20		44
11	16	28	14		40
12	12	16	12		36
13	16	14	10		38
14	18	28	18		54
15	18	8	12		28

when the intravesical pressure is slowly raised to a point which is rather constant for the individual. The vesical volume was increased by adding 2 c.c. of fluid at a time until this overflow occurred. Between each introduction of fluid the intravesical pressure was allowed to fall to a resting level. We felt that a demonstration of increased vesical volume developing coincidently with pregnancy suggested an atony of the vesical musculature such as has been shown for the ureters by Traut.

The rabbits did not stand the repeated administration of an anesthetic well and many were lost during the course of the experiments. For the same reason pregnancy was not often carried to its termination. The edema of the vagina and vulva subsequent to ovulation and during pregnancy was an obstacle to successful catheterization of the urethra.

A few animals developed intractable diarrhea with loss of weight. During the period of diarrhea the vesical volume was increased. Careful records of the weight of the animals were kept from week to week. If a rabbit was losing weight, it was dropped temporarily from the experiment. In general the changes in weight had no correlation with the results. The weights are recorded in the control series shown in Table I.

TABLE I. CASTRATED RABBITS

EXP.	FIRST READING		10-DAY INTERVAL		10-DAY INTERVAL			10-DAY INTERVAL	
	VOL.	WT.	VOL.	WT.	VOL.	WT.		VOL.	WT.
1	8	4.5	24	5.0	12	5.5	Antuitrin-S	18	5.25
2	14	6.0	24	6.75	24	6.75		14	6.5
3	26	5.5	38	6.0	44	6.0		20	6.25
4	16	6.5	22	7.0	10	6.5		14	5.25
5	26	6.0	18	6.5	22	6.5		26	6.75
6	26	5.0	8	5.25	10	5.5		6	5.0
7	48	7.0	26	8.0	26	6.25		18	5.75
8	20	4.75	38	6.0	20	6.25		32	5.75
9	40	3.5	14	4.25	20	5.25		26	5.5
10	30	4.5	20	5.25	32	6.0		30	5.75

EXPERIMENTAL OBSERVATIONS

A. Table I shows the results of a study of ten control animals. The ovaries were removed from the young adult rabbits and they were allowed to recover from the operations. Subsequently a series of four readings of vesical volume was made upon each rabbit at ten-day intervals. After the first three readings the animals were each given 0.2 c.c. of antuitrin-S intravenously. The weight of the rabbit at the time of each reading is given in the chart. According to Dr. Franklin Synder this is sufficient hormone to produce ovulation. It will be observed that the rabbits tended to gain in weight during the progress of the experiment. The readings of vesical volume show only slight variations; ten days after the injection of antuitrin-S no significant changes in vesical volume appeared.

B. The changes in vesical volume associated with pregnancy are shown in Table II. All the rabbits used in the experiments were young virgin females. The records are not complete in all the cases due to difficulty in keeping the rabbits alive and in catheterizing the bladder during pregnancy.

The three control vesical readings are relatively constant for the single individuals. After the third reading the animal was placed with a male. The next reading was made ten days later. Where pregnancy ensued there was in every case an increase in the vesical volume. The normal volume was in several instances doubled or tripled.

Inasmuch as the period of gestation in the rabbit is thirty days it was sometimes possible to make three readings during the period of pregnancy; the results are shown in the tables. As the uterus increased in size there was in certain cases a diminution in the vesical capacity, although the capacity was still much greater than in the nonpregnant animal. Perhaps this was due to mechanical factors pro-

HEMATOMETRA

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HEMATOMETRA is due either to congenital or acquired atresia. Blood retention incidental to menstruation or other bleeding produces distention of the vagina (hematocolpos), uterus (hematometra), and Fallopian tubes (hematosalpinx). Hematovarium and hematoperitoneum also occur.

Since the subject is briefly described in most textbooks and only occasionally referred to in the literature it merits presentation. The interesting pathologic and etiologic aspects, as well as its clinical significance, are discussed on the basis of a group of 19 cases. These represent an incidence of 0.1 per cent of all gynecologic admissions to Mount Sinai Hospital during the years between 1917 and 1937.

In this group, congenital causes of the disease predominate; namely imperforate hymen (10 instances), and bicornuate uterus (1 instance).

CONGENITAL STENOSIS CAUSING HEMATOMETRA

A. *Imperforate Hymen (10 Cases).*—

CASE 1.—Hematocolpos, hematometra, right hematosalpinx.

This 15-year-old patient complained of dysuria for a year. In addition she had backache and abdominal enlargement for one month. Pelvic examination disclosed a blue, bulging, imperforate hymen, and a cystic pelvic mass reaching to the navel. The hymen was excised and the postoperative course was uneventful.

CASE 2.—Hematocolpos and hematometra.

For one year this 16-year-old patient complained of periodic backache. An imperforate bulging hymen and a soft cystic uterus the size of an eight months' gravidity were found. The hymen was excised and trocar drainage instituted.

CASE 3.—Hematocolpos and hematometra.

This 13-year-old patient had backache for eighteen months. For ten days before admission, there was difficulty in voiding. The hymen was imperforate and a cystic uterus of six months' gravidity size was palpable. The pelvic organs returned gradually to normal size after the hymen was excised and the retained blood drained.

CASE 4.—Hematocolpos, hematometra, and hematosalpinx.

Hypogastric distress for two weeks was the only symptom of this 14-year-old girl. There was right rectus spasm and rigidity. The hymen was imperforate, bulging and cyanotic. The uterus reached the umbilicus. A soft mass filled the cul-de-sac. In this case a satisfactory result was obtained after excising the hymen.

CASE 5.—Hematocolpos and hematometra.

The chief complaint of this 17-year-old girl was periodic lower abdominal pain for one year. The hymen was imperforate and bulging; the soft uterus reached to the umbilicus. The hymen was excised and the uterus drained with a hard rubber tube. The uterus contracted immediately to normal state.

DISCUSSION

We have noticed repeatedly in pregnant cats or in animals which had recently been pregnant that the bladder is capable of holding an unusually large quantity of urine so that these animals are not suitable for studies of disturbances of vesical innervation. In the present experiments we have endeavored to put to a test the effect of pregnancy upon the vesical capacity. When the readings were made the rabbits were deeply anesthetized so that the stretch reflex was no longer active, and fluid escaped only by overflow when the organ had reached the limits of its capacity. By three control readings at ten-day intervals in the normal animals we have demonstrated that the vesical capacity remains relatively constant. Ten days after the animals had been with the male and thereafter through pregnancy and the puerperium the vesical volume was increased.

The relationship of the increased vesical volume to changes in the bladder muscle is not established. It seems reasonable to assume that the increased volume is dependent upon decreased tone in the muscle. Microscopic study of the vesical muscle in six animals revealed no significant changes.

The question then arose as to whether ovulation produced similar changes. In ovariectomized rabbits the injection of antuitrin-S had no effect upon vesical capacity. It is therefore reasonable to assume that the anterior pituitary-like sex hormone itself has no direct effect on the bladder muscle. Approximately one-half of the adult virgin rabbits showed a significant increase in vesical volume ten days after the injection of antuitrin-S. These results lead us to assume that a substance is elaborated by the corpus luteum which causes a decrease of tone in the vesical muscle. We are not prepared at the present time to hazard an opinion as to which of the corpus luteum hormones, estrin or progestin, this effect on the bladder muscle tone is due.

These findings are similar to the changes reported in the ureters in women during pregnancy. They make it appear likely that similar changes occur throughout the length of the urinary tract.

Our findings of increased vesical volume following pregnancy confirm the experiments of Woolsey and Brooks. Their results were obtained by quite a different technique. Their findings of diminished volume during estrus or under the influence of progynon-B also lead to the assumption that the sex hormones influence bladder musculature. The fact that progynon-B caused a decrease in bladder capacity suggests that the increased capacity noted by us during pregnancy is due to progesterone rather than estrin.

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patients are not infrequently operated upon for appendicitis. As a rule the patients were afebrile and not acutely ill. Culture of the vaginal blood in several instances was sterile.

Allergic symptoms such as urticaria, pruritus, asthma, and gastrointestinal disturbances (nausea and vomiting) have been reported.

The *signs* are a bulging, cyanotic, imperforate hymen, and a distended vagina upon which may be superimposed a cystic uterus with lateral, tender, sausage-shaped masses. These adnexal masses are usually fixed by adhesions to the lateral pelvic wall or in the cul-de-sac.

The *etiology* of imperforate hymen is still a disputed question. Most authorities favor a congenital origin, while others believe it is acquired.

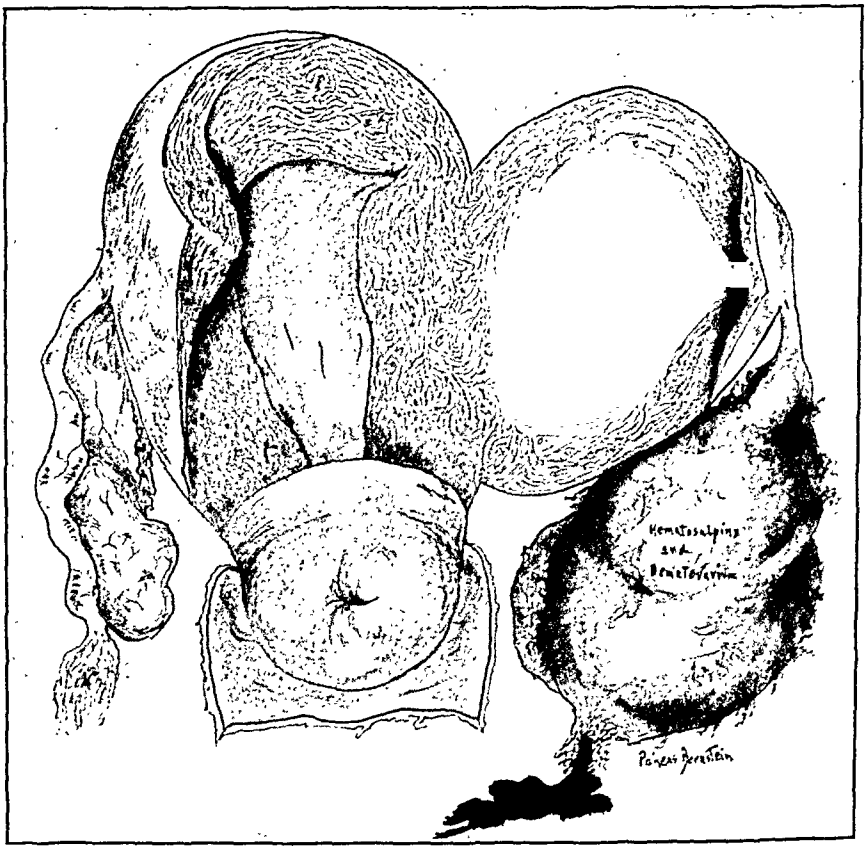


Fig. 1.—Specimen showing blind uterine horn containing hematometra also, hematosalpinx and hematovarium.

In only one of our patients was there a definite history of an acquired cause, namely vaginitis (Case 6). The remaining histories indicate that the origin of imperforate hymen was congenital.

Veit states that a true congenital imperforate hymen produces symptoms in the first six months of life and is due to intrauterine malformation or infection from amniotic fluid. Retained uterine blood, produced by the stimulating action of the maternal female sex hormone on the infantile uterus, causes the hematocolpos and hematometra in the newborn. Moench[16] reported a death in a newborn due to sudden hematometra. Veit also believes that the imperforate hymen producing symptoms at the onset of menses is due to vaginitis acquired

CASE 6.—Hematocolpos.

The history of this 15-year-old girl revealed a vaginitis of four years' duration. Because of inability to void she had been repeatedly catheterized for the month before admission. The hymen was cyanotic and bulging but the uterus was not enlarged. Cure was obtained by excision of the hymen.

CASE 7.—Hematocolpos and hematometra.

Since a hymenoplasty, two years before admission, this 16-year-old girl had intermittent backache. The hymen was cyanotic and bulging. The uterus reached to one inch above the umbilicus. Excision of the hymen produced a cure.

CASE 8.—Hematocolpos and hematometra.

This 13-year-old girl complained of sticking pain in the right lower quadrant of six months' duration, and of continuous lower abdominal pain of two weeks' duration. The hymen was imperforate and the uterus reached to within three fingerbreadths of the umbilicus. Culture of the retained vaginal blood was sterile. The operation was needle aspiration followed by an excision of the hymen.

CASE 9.—Hematocolpos and hematometra.

This 12-year-old girl complained of lower abdominal pain and urinary incontinence of four days' duration. The hymen was bulging and imperforate and the uterus reached to within three fingerbreadths of the umbilicus. The operation consisted of trocar drainage followed by hymenectomy five days later.

CASE 10.—Hematocolpos and hematometra.

This 14-year-old girl complained of backache and intermittent paraumbilical pain of three months' duration. The hymen was bulging and imperforate, the soft uterus reached to within three fingerbreadths of the umbilicus and was asymmetrical. The latter observation suggested the possibility of a hematosalpinx. The operation was hymenectomy.

B. *Bicornuate Uterus.*—

CASE 11.—Uterus bicornis unicollis with ovarian endometriosis.

This 27-year-old nulligravida was married for seven years; and complained of dysmenorrhea, dyspareunia, and continuous pain in the left lower quadrant which increased in severity during the menses. The menstrual cycle was otherwise normal. Pelvic examination disclosed a one finger nulliparous introitus with marked vaginismus. The uterus was enlarged and bilobed and a tender mass arising from its left tubal angle was fixed to the lateral pelvic wall. The preoperative diagnosis was fibroid uterus and left ovarian cyst. The left adnexa and a left rudimentary uterine horn were removed. The operative findings were a bicornuate uterus with a small hematometra in the blind rudimentary left horn. The tube and ovary could not be identified as both were involved in a cystic mass containing old blood which was firmly adherent to the left pelvic wall. (Fig. 1.)

The specimen disclosed a small uterine body the cavity of which was continuous only with the left tube and the ovarian endometrial cyst. It had no connection with the main uterine cavity.

SIGNS AND SYMPTOMS

All but the last patient were between 12 and 16 years of age and had never menstruated. The most common complaint was pain; the sites of which in the order of frequency were low-back, abdominal, and suprapubic. Four patients had urinary complaints as dysuria, retention, or incontinence due to urethral and bladder compression from a distended vagina and uterus.

Incontinence results from overflow. Two of the patients had pain and tenderness with muscle spasm in the right lower quadrant. These

Adhesions fixing the distended paper-thin tubes to the pelvic wall add the danger of rupture, hemorrhage, and shock during sudden emptying or manipulation from below. Blood furnishes a fertile culture medium for bacteria which may penetrate the adherent intestinal wall or ascend from below. Rapid and fatal peritonitis may result. Subdiaphragmatic gravitation of blood is common. As much as 3.5 liters of bloody fluid have been removed (R. T. Frank quotes T. Wright[5]).

Hematometra with pelvic endometriosis occurred only twice in our patients. Although these findings support the endometrial displacement theory of Sampson, endometriosis should be a more frequent complication of gynatresia since reflux tubal bleeding is common.

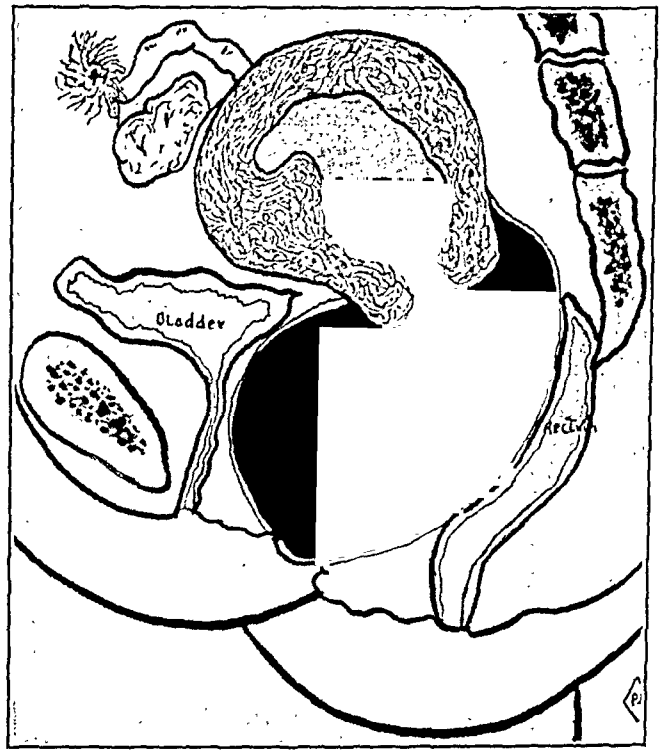


Fig. 3.—Advanced hematocolpos and hematometra due to imperforate hymen.

The end stage of hematometra is characterized by a compression of glandular, vascular, and structural elements (Fig. 4). The inner lining of the entire genital tract is flattened into a single epithelial layer, which permits later regeneration. The entire genital system, by distention, is finally converted into a thin-walled bulbous sac.

The character of the hematometra fluid varies with the patient's age and the site of atresia. During infancy and prepuberty, mucus is conspicuous; in mature patients menstrual elements are the chief constituents, and during the menopause debris and blood (not menstrual) are found. Cervical and vaginal secretions are manifest in all periods but are increased during maturity.

The laked red blood cells are the chief constituents. Lactic acid without the lactic acid bacillus, and mucin, are found. The fluid has a high calcium content but no fibrinogen or fibrin is present. Although

during childhood. Vaginitis may be secondary to an acute febrile illness, such as scarlet or typhoid fever or result from irritating urine or feces. The gonococcus is a well-established offender.

A short statement concerning the development of the female genital tract provides a clearer understanding of congenital malformations. The female reproductive organs are derived from the Müllerian ducts and urogenital sinus. The former are entirely retained; fusion of the lower portions forms the vagina and uterus, while the upper paired free parts give rise to the Fallopian tubes. The lower third of the vagina, however, arises together with the vulva from ectoderm; their point of junction is the most frequent site of malformation (imperforate hymen).

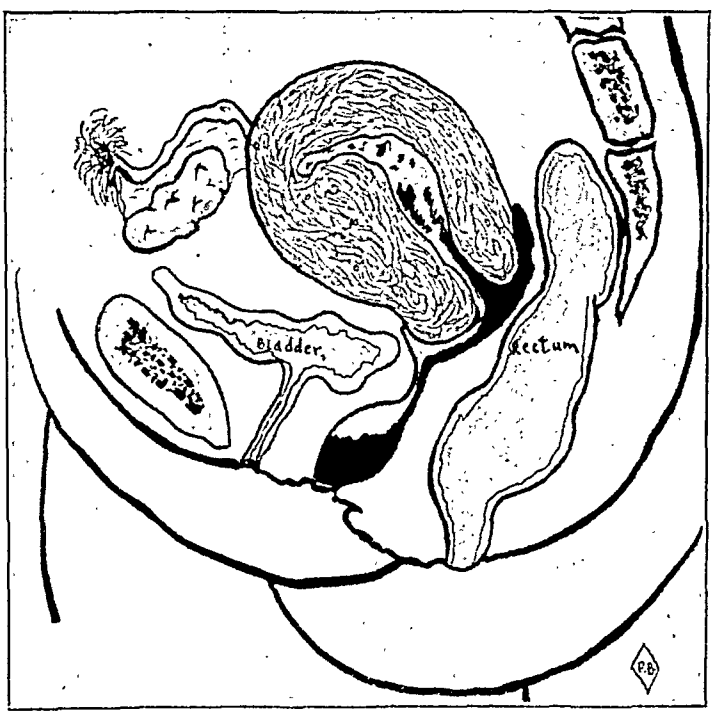


Fig. 2.—Early stage hematocolpos and hematometra due to imperforate hymen.

The pathogenesis of hematometra is completely illustrated by an imperforate hymen obstruction (Fig. 2). At first the vagina becomes moderately dilated by collections of blood and, as maximal distention is produced by further bleeding, the uterus rides above the hematocolpos (Fig. 3). A vulvoperineal prominence appears, the labial folds separate and the bulging, tense, cyanotic, imperforate hymen is exposed. If the latter ruptures spontaneously, the ascending process terminates; if not, the uterine corpus dilates and finally the cervix. Eventually blood, forced into the tubes, escapes into the peritoneal cavity, producing varying degrees of hematosalpinx followed by hematoperitoneum. Pyopneumohematometra and pyopneumohematosalpinx may result if the fimbriated tubal end is closed. The mechanism of closure is identical with that seen in salpingitis (infection) or in ectopic gravidity (aseptic).

B. *Instrumental Delivery and Post-Partum Infection, Causing Cervical Stenosis.*—

CASE 13.—This 42-year-old patient, ten months prior to admission, had an instrumental delivery of a full-term stillbirth followed by a mild post-partum infection. Regularly since then her periods were two days to two weeks in duration. A lacerated clean cervix and a normal-sized uterus were found. Partial obstruction of the cervix was encountered at operation and following complete dilatation a moderate amount of old blood escaped. The diagnosis was partial cervical stenosis and hematometra.

C. *Repair of Post-Partum Vesicovaginal Fistula, Causing Cervical Stenosis.*—

CASE 14.—This patient was a 25-year-old gravida ii, para i. Her chief complaint was periodic attacks of suprapubic and low back pain of one and one-half years' duration. Nine years before admission she was delivered of a full-term macerated fetus and sustained a vesicovaginal fistula and third-degree perineal tear. These were repaired one year after the injury. Patient had amenorrhea following delivery which persisted until three days prior to admission when slight bleeding occurred. Pelvic examination revealed a stenosis of the cervix and a soft, cystic uterus enlarged to the size of a three and one-half months' gravidity. At operation the uterus contained 120 c.c. of old blood. There was a right hematosalpinx and a cystic right ovary. The uterus was adherent to the cul-de-sac posteriorly and the bladder anteriorly. A supravaginal hysterectomy and a right salpingo-oophorectomy were performed. Culture of the retained uterine blood was sterile. The postoperative course was uneventful and the patient was discharged fourteen days after operation. Final diagnosis was hematometra and right hematosalpinx secondary to cervical stenosis.

D. *Hematocolpos Secondary to Post-Partum Vaginal Atresia.*—

CASE 15.—This patient, a 22-year-old gravida i, para i, was delivered instrumentally of a stillborn full-term fetus three months prior to admission. Following this she had amenorrhea and continuous urinary incontinence. Pelvic examination disclosed a short vagina with obliteration of the fornices by adhesions. Neither cervix nor uterus could be identified. There was a 3 cm. opening in the anterior vaginal wall which communicated with the bladder. Preparatory to the repair of the vesicovaginal fistula, an attempt was made to release the adhesions in the upper part of the vagina and during this procedure a blind cavity was entered and 8 or 9 drams of old blood escaped.

E. *Cervical Stenosis Following Removal of Cervical Fibroadenoma and Dilatation and Curettage.*—

CASE 16.—This patient was a 43-year-old gravida and para ii who complained of severe abdominal pain, radiating to the back and thighs. She had had a posterior colporrhaphy, appendectomy, ligation of tubes and ventral fixation, followed two years later by a dilatation and curettage for a fibroadenoma of the cervix. Pelvic examination disclosed a completely stenosed cervix and a tense cystic uterus the size of a three months' gravidity. At operation the uterus contained old blood but both tubes and ovaries were normal. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful.

F. *Cervical and Vaginal Stenosis Following X-ray and Radium Therapy for Carcinoma of the Cervix.*—

CASE 17.—This 65-year-old woman complained of a painless enlarging, pelvic mass. Her menopause began fifteen years before. Following the diagnosis of carcinoma of the cervix she received x-ray and radium therapy; the exact dosage was not mentioned. Pelvic examination revealed a large cystic, symmetrical mass rising out of the pelvis to four fingerbreadths above the umbilicus. The vagina was completely obstructed by adhesions. At operation a panhysterectomy was performed and a huge distended uterus which contained 800 c.c. of blood was removed. Microscopic study of the uterus showed atrophic mucosa with transitional and squamous cell metaplasia. The postoperative course was uneventful.

G. *Menopausal Cervical Stenosis and Adenomyosis Uteri.*—

CASE 18.—This 51-year-old gravida and para iv had meno-metrorrhagia and lower abdominal pain on the first day of the period, for two years. Her last

usually sterile the fluid may contain *B. coli* and other organisms which are secondary invaders from blood or lymph streams, from adherent intestine, or are introduced during surgical intervention. The fluid, if infected, is malodorous, purulent, and hemorrhagic, and drains slowly because of its treacle-like consistency. Although the usual amount is 500 to 1,500 c.c., as much as 3,500 c.c.[15] have been evacuated. The color varies from bright red to black. Fluid obtained from 5 cases of hematometra has been assayed for female sex hormone. An estrogenic reaction was present in only one (personal communication from R. T. Frank).

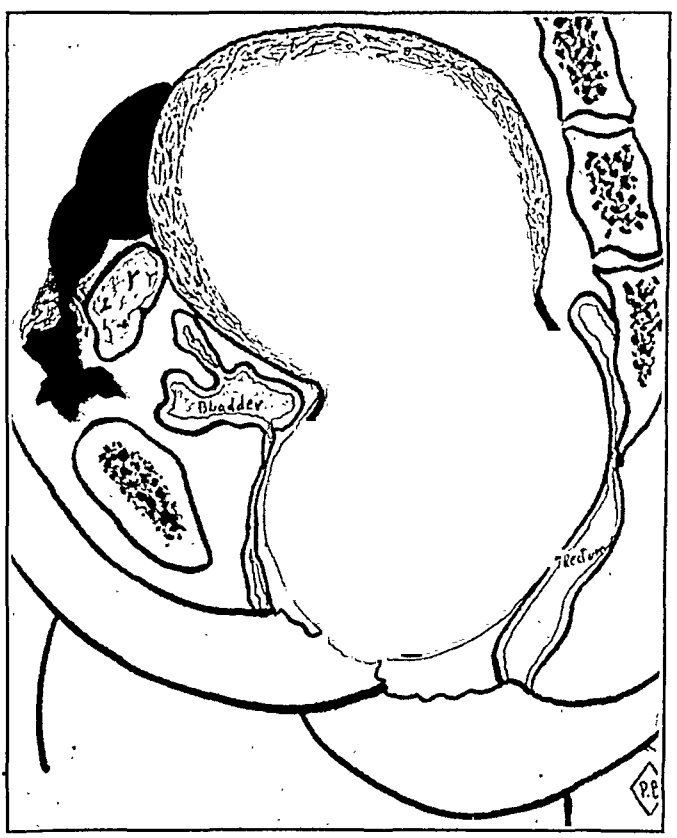


Fig. 4.—Late stage showing hematocolpos, hematometra, and hematosalpinx due to imperforate hymen.

ACQUIRED STENOSIS CAUSING HEMATOMETRA

A. *Cervical Stenosis Due to Cauterization.*—

CASE 12.—This 43-year-old patient, gravida x, para vi, had 4 induced abortions. Her chief complaints were amenorrhea, abdominal pain, urinary urgency, and frequency. The cervix was cauterized one year prior to admission. Pelvic examination disclosed a stenosed cervix which did not permit the passage of a fine probe; a slightly enlarged uterus; and bilateral tender, cystic adnexal masses. At operation, the uterus was found to be enlarged to the size of an eight weeks' gravidity by old blood, and there were also bilateral ovarian cysts and hematosalpinges. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed with drainage through the cervix. The pathologic report was "cervical stenosis, chronic hematometra, bilateral hemorrhagic endometrial cysts of the ovaries, and adenomyosis of the uterus." The patient, febrile for ten days postoperatively, was discharged on the eighteenth day.

adenocarcinoma on the lateral uterine wall. The operation consisted of a supravaginal hysterectomy and a bilateral salpingo-oophorectomy. A small fibroadenoma of the cervix protruded into the cervical canal, causing partial obstruction.

The most common cause of stenosis in this group of cases was injury sustained during delivery, followed by infection (Cases 13, 14, and 15). Cervical stenosis secondary to cervical fibroadenoma was encountered twice (Cases 16 and 19). The other etiologic factors were cauterization of the cervix, x-ray therapy, and involutional cervical changes. Caustics, hyperpyrexia, stem pessaries, gonorrheal and diabetic vaginitis have also been reported.

The syndrome in the female at puberty is generally similar to that in older women, except that in later life the history indicates an acquired cause for the condition. Since at first the acquired stenosis is usually partial, the pelvic organs do not show marked enlargement. A prolonged, diminished, black, tarry flow and occasionally metrorrhagia characterize the menses, and as the block becomes complete, amenorrhea and painful genital tract distention set in. Occasionally dyspareunia occurs.

Acquired hematometra is usually unrecognized until ushered in by general malaise, chills and high fever due to presence of infection. As a rule, however, the general health is not affected and constitutional changes arise only with hemorrhage and infection. A correct preoperative diagnosis in this type of patient is rarely made.

In uncomplicated cases of hematometra and hematocolpos the temperature, pulse, and respiration, as well as blood count and sedimentation time, are within normal limits. When the pain localizes in the right lower quadrant, appendicitis is usually first considered. Congenital anomalies always complicate the picture. A double uterus is confusing, since one uterus may bleed normally or may be enlarged by a fetus, while the other, due to atresia, may contain a hematometra. Pregnancy is simulated by the moderately enlarged, soft uterus, and amenorrhea, and abortion by the intermittent uterine bleeding.

Ectopic pregnancy is suspected in cases of unilateral ruptured hematosalpinx. The amenorrhea, and sudden pelvic pain radiating to the shoulder or subdiaphragmatic region in a patient with an adnexal mass, a soft uterus, rapid pulse (and shock) are identical with the clinical picture of a ruptured ectopic pregnancy.

The treatment of gynatresia is always surgical. The extent and method of the surgical procedure depend on the site and type of atresia, the patient's age, the necessity for preserving the childbearing function, and the presence or absence of infection. The prevention of secondary infection and the establishment of free but slow drainage are the fundamental principles involved. Simple procedures were usually adequate in the younger patients of this group.

Conservatism was employed, particularly in children, since risks of laparotomy and the undesirable effects of castration and sterilization contraindicate radical surgery except as a lifesaving measure. In older women, especially at the climacterium, radical measures were

menstrual period occurred two months prior. On admission she complained of severe generalized abdominal pains which within twelve hours had localized in the right lower quadrant. There was also moderate uterine bleeding. Physical examination disclosed an acutely ill patient in moderate shock. The blood pressure was 84/54. There was marked bilateral adnexal tenderness. The pelvic organs could not be definitely outlined because of the spasm. Exploratory laparotomy revealed a small amount of blood in the pelvis and under both leaves of the diaphragm. The uterus was soft, cystic and distended to the size of a three months' gravidity. Bilateral hematosalpinges were present. A panhysterectomy was performed. The pathologic report was partial stenosis of the cervix at the internal os; adenomyosis of the uterus; hematometra; bilateral hematosalpinx and hematoperitoneum. The postoperative course was uneventful (Fig. 5).

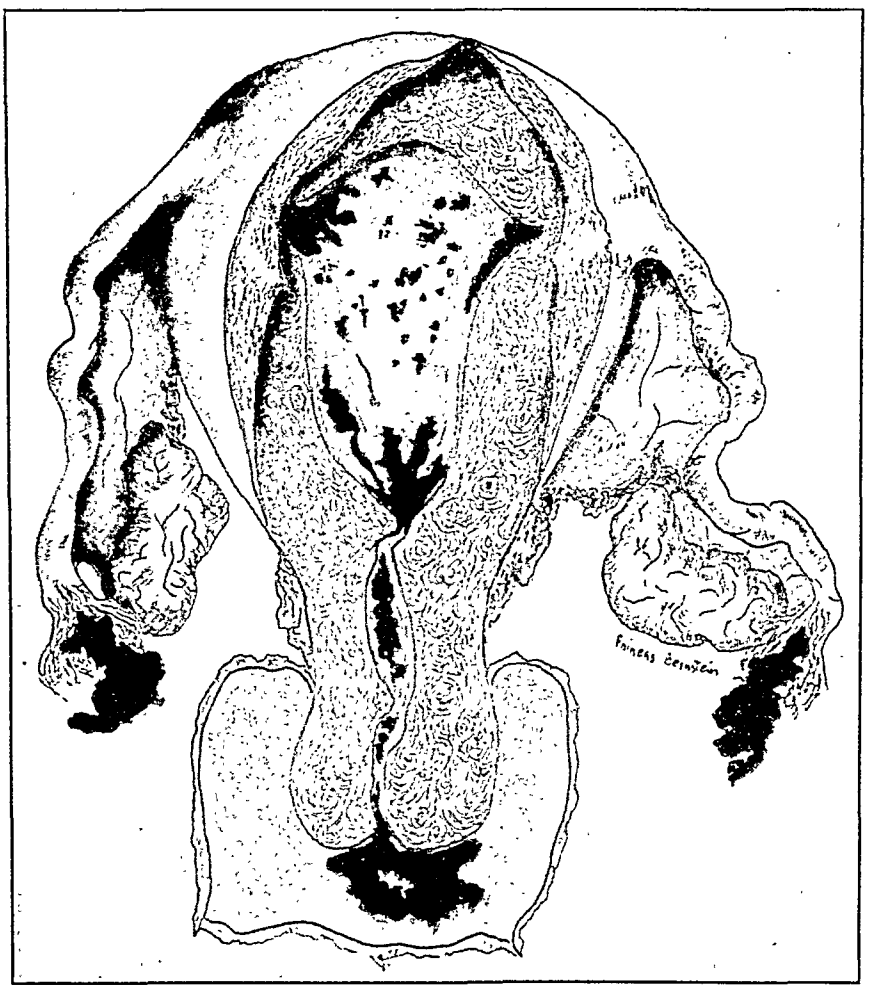


Fig. 5.—Partial cervical stenosis and endometriosis causing partial hematometra, hematosalpinx, and hematoperitoneum.

H. *Cervical Obstruction Secondary to Uterine Fibroids.*—

CASE 19.—This patient was 78 years of age. The climacteric had occurred at the age of 40. Her chief complaint was metrorrhagia of five weeks' duration. In addition she mentioned a large pelvic mass the size of which was constant for the past thirty years. Pelvic examination disclosed a senile atrophic vagina and an irregularly enlarged firm uterus reaching one fingerbreadth above the umbilicus. The sedimentation time was accelerated to fifteen minutes. Dilatation and curettage disclosed a huge distended uterine cavity; but the curettings *showed grossly no evidence of carcinoma.* When the pelvis was explored, a large distended fibroid uterus containing old clotted blood was found. The opened cavity revealed a large, oozing,

SUMMARY

1. Nineteen cases of hematocolpos and hematometra are discussed. Eleven were due to congenital anomalies and 9 were secondary to acquired gynatresia.

2. Imperforate hymen is the most frequent congenital anomaly producing hematometra.

3. The etiologic factors causing acquired atresias are childbirth injuries and post-partum infection. Cervical cauterization, x-ray therapy, atrophic changes, and cervical tumors also cause stenosis leading to hematometra.

4. In children, the diagnostic triad is an imperforate bulging hymen, a pelvic tumor and delayed menses.

5. In adults, diagnosis is not as simple, since the gynatresia is usually acquired and partial. Large hematometra are therefore rare.

6. Treatment is always surgical. Conservatism is advocated.

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2 East 85th Street

Ketteringham, Rose C., and Austin, Bruce R.: Blood Sugar During Labor, at Delivery and Postpartum, With Observations on Newborns, Am. J. M. Sc. 195: 328, 1938.

The mean maternal blood sugar at delivery in 50 cases was 124.6, with 60 per cent of the cases falling between 110 and 140 mg. per 100 c.c., approximately 40 to 50 mg. above the normal range. The mean blood sugar for 47 infants at birth was 103.6; 94 per cent of these infants presented values lower than those of their respective mothers. Both anesthesia and labor have been shown to contribute to the rise in blood sugar at delivery, but there is no indication that the duration of these factors is the primary cause of the rise. The blood sugar of the infant is dependent upon that of its mother, and factors affecting the blood sugar of the mother affect that of the infant. It would seem that the newer obstetric techniques produce no deleterious effects on the glucose metabolism. In 28 cases, comparison showed the blood sugar higher at delivery than during the first stage by a difference in mean of 28 mg. per 100 c.c. The blood sugar of any particular individual two or three days post partum is somewhat higher than normal. The authors established the normal blood sugar range for newborns by the modified Folin-Malmros technique. The first two days of life the blood sugar is 55 to 85 mg. per 100 c.c., with slightly higher values on the third day. Within three to six hours after birth the blood sugar drops to the normal infant range.

J. Thornwell Witherspoon.

more reasonably utilized, since benign and malignant tumors often found complicating the hematometra necessitated panhysterectomy; infection, often present, required adequate drainage.

For imperforate hymen, we found complete excision most satisfactory, since there was little danger from sepsis or recurrence. The free double margins of the excised hymen are sutured with interrupted chromic catgut. Patients are kept in bed postoperatively for ten to fourteen days, preferably in Fowler's position to further drainage.

Promoting uterine involution by vaginal tampon, trocar, irrigation, aspiration, and emmenagogues is to be condemned. Pelvic examinations after operation were not performed. Crucial incision of the hymen has fallen into disrepute, since it is followed by recurrence.

Obstructing vaginal septa and membranes are completely excised. Hematometra with vaginal atresia requires a hysterectomy. If construction of an artificial vagina is necessary it may be undertaken later. The skin tube-flap operation devised by Frank and Geist[6] has been used successfully.

For cervical atresias careful dilatation or anterior lip incision are indicated: a rubber tube is inserted into the uterine cavity for drainage. The cervix should be manipulated carefully to avoid rupture of an unrecognized hematosalpinx.

Unilateral hematometra and hematosalpinx in a bicornuate uterus were treated by amputation of the affected side.

Generally the surgeon is guided by the exigencies of the situation when complicated pelvic anomalies are found.

Hematosalpinx is serious due to a potential, if not already present, infection, and most authorities advise an exploratory operation. Since the atresia must also be removed, the problem arises as to which procedure should be done first, the vaginal or abdominal. The advantages of doing the vaginal operation first are: (1) The true pelvic status is more easily and accurately determined after evacuation of vaginal and uterine blood, and (2) if supravaginal hysterectomy is necessary later, abdominal spill of infected blood from vagina and uterus is avoided (Graves).

On the other hand "if the hematosalpinx has already developed, drainage from below will be a real danger on account of an ascending infection" (Reinert). Also bimanual examination following the evacuation of blood from the vagina and uterus may light up a dormant infection or introduce it to the adnexa from below.

Since drainage from below is most often effective in our experience, it is always indicated first in the absence of clinically infected hematosalpinges. However, the patient should be carefully observed for complications. Thus, a laparotomy and the certain loss of part, if not all, of the pelvic organs is avoided. We believe that vaginal examinations are to be avoided whenever possible.

If serious complications have already occurred, such as hemorrhage, peritonitis or tuboovarian abscess, intervention by laparotomy is necessary. Drainage is advisable in these cases because of the accompanying infection.

addition, a large number of men handle the private service and some of them are probably less conservative in their private cases than we are in managing ward cases.

Table III is a composite of the series here reported and the series reported a few years ago, showing a comparison of incidence and mortality for different time periods.

TABLE III

YEARS	DELIVERIES	SECTIONS	INCIDENCE	DEATHS
1908-1916	4,116	122	1:33.7 (3.0%)	1 (0.82%)
1916-1924	7,637	237	1:32.2 (3.1%)	12 (5.1%)
1924-1932	17,425	374	1:46.5 (2.2%)	12 (3.2%)
1932-1937	11,210	380	1:30 (3.3%)	8 (2.1%)
Total	40,388	1,113	1:36 (2.7%)	33 (2.9%)

In the 380 sections done during the last five years, the incidence of 3.3 per cent is certainly greater than in any one of the three other periods shown in the previous table. We believe the reason to be that we are today doing many more sections for placenta previa, cardiac disease, and progressive toxemia, than we used to do in the past. This is brought out rather strikingly in Table IV.

TABLE IV

YEARS	NO. OF SECTIONS	FOR TOXEMIA	FOR PLACENTA PREVIA	FOR CARDIAC CONDITIONS
1908-1932	733	37 (5.0%)	19 (2.6%)	18 (2.5%)
1932-1937	380	32 (8.4%)	24 (6.3%)	24 (6.3%)

2. INDICATIONS FOR SECTIONS

Table V gives the indications in the order of their frequency together with the maternal and fetal mortality for each group. The fetal deaths do not include nonviable fetuses. In cases where several factors indicated the necessity for cesarean section, the most important one is classified as the indication.

Disproportion, either with normal or with contracted pelvis, was responsible for 35.7 per cent of the total number of sections. In this group there was a maternal mortality of 1.4 per cent, and no fetal mortality.

Previous cesarean section was the second largest group with 88 cases or 23.1 per cent; the maternal mortality in this group was 1.1 per cent and the fetal mortality 3.3 per cent. While some clinics allow selected cases to go through labor after previous section, at our hospital we prefer to handle these cases by elective section, usually with sterilization if the woman has one or more living children.

Progressive toxemia, placenta previa, cardiac disease with a history of broken compensation, and previous stillbirths, account for 26 per cent of the cases. During the past five years the percentage of cases handled by section for these four indications has been greater than at any other time in the history of the hospital.

A REVIEW OF CESAREAN SECTIONS

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OUR object in presenting this paper is to add 380 cases done during the last five years (1932 to 1937) to our previously reported series of 733 cases; thus giving us a large series (1,113 sections) for study and analysis. This study gives us an opportunity to compare the results of the past five years with those reported in our previous communication: as to incidence, morbidity, mortality, and comparative results for classical and low flap sections. The latter operation was done only rarely prior to 1932 but since then has been performed quite frequently.

1. INCIDENCE

During the five-year period, 1932 to 1937, 11,210 women were delivered at our hospital. Of these, 380 or 3.3 per cent, had a cesarean section. Table I gives the number of deliveries, the number of sections, and the deaths following section for each year of the five-year period.

TABLE I

YEAR	NO. OF DELIVERIES	CESAREAN SECTIONS	DEATHS FOLLOWING SECTION
1932	2,416	72	0
1933	2,259	72	1
1934	2,350	92	0
1935	1,947	74	4
1936	2,238	70	3
Total	11,210	380	8

We further divided this series of cases into two groups: private and general service. There were 7,932 private cases with 297 sections; an incidence of 3.7 per cent or 1 in 27 cases. The number of general service cases was 3,278 with only 83 sections; an incidence of 2.5 per cent or 1 in 40 cases. These facts are shown in Table II.

TABLE II

	NO. OF CASES	SECTIONS	INCIDENCE
Private Cases	7,932	297	3.7% or 1 in 27
Ward cases	3,278	83	2.5% or 1 in 40
Total	11,210	380	3.3% or 1 in 30

We feel that the reason for the greater incidence of sections in private cases as compared with the ward service is that most of the repeat sections, and a large percentage of the cases done for advanced cardiac disease and previous plastic operations are from the private service. In

TABLE VI. CAUSES OF MORBIDITY (IN TERMS OF PATHOLOGY)

Wound infections	53 cases
Endometritis	31 cases
Upper respiratory infection	10 cases
Phlebitis	10 cases
Sepsis	6 cases
Generalized pelvic infection	6 cases
Parametritis alone	5 cases
Pyelitis	7 cases
Postpartum hemorrhage	4 cases
Acute cholecystitis	1 case
Cystitis	1 case
Pulmonary collapse	1 case
Pulmonary infarct	2 cases
Degeneration of fibroid	2 cases
Vesicovaginal fistula	1 case
Omental abscess	1 case
Bilateral parotitis	1 case

compared with the total number morbid in terms of temperature alone. The relationship between morbidity and type of anesthesia will be discussed later. Associated procedures such as sterilization, myomectomy, occasional hysterectomy, and repair of abdominal hernia, seem to have little or no effect on morbidity.

Table VII shows the relation of duration of ruptured membranes, length of labor, and number of vaginal examinations, to average morbidity (number of days of elevated temperature).

TABLE VII

MEMBRANES		HOURS IN LABOR		VAGINALS	
CONDITION	AVERAGE MORBIDITY	NO. OF HOURS	AVERAGE MORBIDITY	NO. OF VAGINALS	AVERAGE MORBIDITY
Intact	3.5 days	0-12	3.6 days	None	3.8 days
Ruptured 1 to 12 hr.	5.2 days				
Ruptured 12 to 24 hr.	5.0 days	12-48	7.1 days	1 or 2	8.7 days
Ruptured 24 to 48 hr.	7.2 days				
Ruptured 48 hr. and over	15.6 days	Over 48	8.3 days	3 or more (only 2 cases)	6.5 days

Table VII corroborates the well known fact that the longer the membranes are ruptured and the longer the patient is in labor before section is done, the greater the morbidity.

4. MATERNAL MORTALITY

In the series of 380 sections, eight mothers died, giving a maternal mortality of 2.1 per cent. This is lower than the previous mortality rate of 3.4 per cent reported by us in our series of 733 cases.

CASE 1.—(1933.) A primipara with double mitral disease and a history of broken compensation before and during pregnancy. Membranes ruptured eight hours; mild pains for seven hours. Classical section with sterilization under local anesthesia supplemented by gas-oxygen inhalation anesthesia. Eviscerated on sixth day postoperative. Wound resutured. Died of general peritonitis on twentieth day after section.

TABLE V

INDICATION	NO. OF CASES	MATERNAL DEATHS	FETAL DEATHS
A. Disproportion	*136* (35.7%)	*2* (1.4%)	*0*
a. With contracted pelvis	96	2	0
b. With normal pelvis	40	0	0
B. Previous cesarean section	*88* (23.1%)	*1* (1.1%)	*3* (3.3%)
C. Toxemias	*32* (8.4%)	*0*	*4* (25.0%)
a. Eclampsia and pre-eclampsia	23	0	3
b. Chronic nephritis	8	0	1
c. Marked essential hypertension	1	0	0
D. Placenta previa	*24* (6.3%)	*1* (4.1%)	*2* (8.3%)
E. Cardiac disease	*24* (6.3%)	*1* (4.1%)	*0*
F. Previous stillbirths	*19* (5.0%)	*0*	*0*
G. Soft part dystocia (operative)	*14* (3.6%)	*1* (7.2%)	*0*
a. Previous myomectomy	8	1	0
b. Vaginal plastics	6	0	0
H. Malposition	*10* (2.6%)	*0*	*0*
a. Breech	7	0	0
b. Transverse	3	0	0
I. Uterine inertia and cervical dystocia	*10* (2.6%)	*0*	*0*
J. Soft part dystocia (nonoperative)	*6* (1.5%)	*0*	*0*
a. Fibroids	4	0	0
b. Double uterus	2	0	0
K. Old primipara with long history of sterility	*6* (1.5%)	*1* (16.6%)	*0*
L. Diabetes	*4* (1.0%)	*0*	*0*
M. Ruptured uterus	*2* (0.5%)	*0*	*2* (100.0%)
N. Ablatio placentae	*2* (0.5%)	*0*	*1* (50.0%)
O. Contraction ring	*1* (0.2%)	*1* (100.0%)	*1* (100.0%)
P. Fractured pelvis	*1* (0.2%)	*0*	*0*
Q. Ectopic kidney in pelvis	*1* (0.2%)	*0*	*0*
Total	380	8	13

The remaining 15 per cent of the sections were done for a great variety of indications as shown in Table V.

3. MORBIDITY

Any patient who had a temperature over 100.0° F. by mouth for more than 72 hours postoperatively was considered morbid. Of the 372 patients who lived, 173 or 46.5 per cent were morbid. This is practically the same as the morbidity of 46.8 per cent reported for our previous series of 733 sections. There is always a marked discrepancy between the classification of morbidity in terms of temperature alone, and morbidity in terms of actual pathology. A good many patients run an elevated temperature for four or five days and yet no definite cause can be found to account for it. Other cases may have a wound infection or a severe postpartum hemorrhage or a low grade endometritis with foul lochia and yet have a perfectly normal temperature. Table VI gives the causes of morbidity in terms of actual pathology.

A good many of the cases in Table VI overlap; e.g., the patient who has a generalized pelvic infection may also have an upper respiratory infection and a wound infection; and such a patient would be charted in all three categories. Thus, the number of patients whose morbidity is explainable in terms of actual pathology, is really quite small when

5. FETAL MORTALITY

The gross or total fetal mortality was 21 or 5.5 per cent. Correcting for nonviability, the fetal mortality is reduced to 3.4 per cent.

TABLE IX. FETAL MORTALITY

	TOTAL	NONVIABLE FETUSES	CORRECTED
Stillbirths	10	5	5
Neonatal deaths	11	3	8
Total	21 (5.5%)	8	13 (3.4%)

The gross or total mortality includes stillbirths and neonatal deaths. The only correction made is for nonviability (all fetuses less than twenty-eight weeks old were considered nonviable).

Stillbirths.—Of the 10 stillbirths, 5 were nonviable and 5 were full term. Of the viable stillbirths, two mothers were sectioned for ruptured uterus, one for previous section, one for ablatio placentae and one for contraction ring. Of the 5 nonviable stillbirths, one mother was sectioned for essential hypertension with myocarditis, two for chronic nephritis, and one for advanced cardiac disease (twins).

Neonatal Deaths.—There were 11 babies that died in the first two weeks of life. Of these 3 were nonviable. Of the 8 viable ones, five died of prematurity, two died of pulmonary atelectasis, and one of pulmonary atelectasis associated with multiple visceral hemorrhages.

6. ELECTIVE SECTIONS

One hundred twenty-five patients were sectioned before the onset of labor, with membranes intact, and in the vast majority no vaginal examination was done. One mother died (see Case 5 under maternal mortality), giving a mortality of 0.8 per cent. This group of cases does not include cases of eclampsia or placenta previa.

Forty patients were morbid, an incidence of 32.2 per cent. The morbidity for the entire group of 380 cases was 46.2 per cent.

In our previous series of 733 sections there were 152 elective sections with 3 deaths, giving a 1.9 per cent maternal mortality. Adding the two elective groups together we have 277 sections with 4 deaths, a 1.4 per cent mortality rate. This group of elective cases gives us our lowest mortality. For the 836 nonelective sections (total of both groups) our maternal mortality was 3.4 per cent.

Of the 125 elective cases done from 1932 to 1937 about 50 per cent were done for previous section, about 25 per cent for progressive toxemia, nephritis, and cardiac disease, 10 per cent for previous stillbirths, and the remainder for such indications as deep myomectomy, complete vaginal plastics, abruptio placentae, multiple fibroids, diabetes, etc.

The gross fetal mortality for these 125 elective sections was 10 or 8 per cent; of the 10 babies 6 were nonviable, giving a corrected fetal mortality of 3.2 per cent which is practically the same as the 3.4 per cent corrected fetal mortality for the entire group.

CASE 2.—(1935.) A gravida iv, para iii, with membranes ruptured forty-one hours; in labor thirty-seven hours; three vaginal examinations. Vaginal delivery attempted by forceps after bilateral cervical incisions. This failed. A tentative diagnosis of ruptured uterus was made. Two hours later a Porro section was done under local infiltration anesthesia. Uterus found unruptured; marked retraction ring present. Died of peritonitis on sixth day.

CASE 3.—(1935.) A 35-year-old primipara with a history of sterility of fifteen years; membranes ruptured seven hours; no pains; one vaginal examination. A low flap section done under gas-oxygen-ether inhalation anesthesia. Died of a virulent peritonitis in forty-eight hours.

CASE 4.—(1935.) A 32-year-old primipara with a generally contracted pelvis. Membranes intact; no vaginal examinations; mild pains for fifteen hours. Low flap section under spinal anesthesia. Died of peritonitis on sixth day.

CASE 5.—(1935.) A 31-year-old primipara who had had a deep myomectomy in 1930. Elective low flap section under general anesthesia. Marked bleeding during operation. Patient rapidly went into deep shock and died six and one-half hours after operation in spite of shock treatment and transfusion. Fifteen minutes before death, patient expelled about 800 c.c. of blood vaginally, indicating that there had probably been marked uterine atony with intrauterine hemorrhage.

CASE 6.—(1936.) A 29-year-old gravida ii with a generally contracted pelvis. Membranes intact; no vaginal examinations; mild pains for five hours. Classical section under gas-oxygen-ether anesthesia. Eviscerated on sixth day. Wound resutured; plastic peritonitis found. Died on sixth day, a few hours after resuturing of wound.

CASE 7.—(1936.) A 34-year-old gravida ii with history of previous section. Membranes ruptured thirteen hours; no vaginal examinations; no pains. Low flap section and sterilization under gas-oxygen-ether anesthesia. Died on fifth day of symptoms suggesting pulmonary embolus.

CASE 8.—(1936.) A 30-year-old primipara with a partial placenta previa. Classical section under gas-oxygen-ether anesthesia. Had a small pulmonary embolus on twelfth day postoperative, resulting in a pulmonary infection. Discharged from hospital on twenty-second day while still running a low grade temperature of 100.0° F. Died suddenly after three days at home. Death probably due to a large pulmonary embolus.

TABLE VIII. MATERNAL MORTALITY

CAUSE OF DEATH	NO. OF CASES	INDICATION FOR SECTION	
Peritonitis	5	Contracted pelvis	2
		Cardiac disease	1
		Contraction ring	1
		Old primipara	1
Pulmonary embolus	2	Placenta previa	1
		Previous section	1
Shock—probably due to uterine hemorrhage	1	Previous deep myomectomy	1

Infection and embolus are responsible for 87.5 per cent of the deaths. In our previous series they accounted for 84 per cent of the deaths.

A study of the condition of the membranes, duration of labor, and number of vaginal examinations in the 8 patients who died, fails to reveal any definite relationship between these factors and the death of the patient. The same was true for the 25 deaths in our previous series of sections. However, it is quite likely that in a very large series of deaths following section, some definite relationship could probably be established.

TABLE XII. COMPOSITE TABLE FOR 1,113 SECTIONS 1907 TO 1937

INCIDENCE			MATERNAL MORTALITY			MORBIDITY			FETAL MORTALITY (CORRECTED)			MORTALITY ELECTIVE SECTIONS			TYPE OF SECTIONS					
															CLASSICAL			LOW FLAP		
DELIVERIES	SECTIONS	PER CENT	SECTIONS	DEATHS	PER CENT	SECTIONS	MORBID	PER CENT	SECTIONS	FETAL DEATHS	PER CENT	ELECTIVE SECTIONS	DEATHS	PER CENT	945	DEATHS	PER CENT	168	DEATHS	PER CENT
40,388	1,113	1:36 2.7%	1,113	33	2.95	1,113	505	45.3	1,113	40	3.5	277	4	1.4		28	2.96		5	2.97

7. TYPE OF OPERATION

Of the 380 cases for 1932 to 1937, 269 sections were of the classical type with 5 deaths, giving a maternal mortality of 1.8 per cent. One hundred and eleven were low flap sections with 3 deaths, a mortality rate of 2.7 per cent. If we add together the classical and low flap sections for the entire series of 1,113 cases from 1907 to 1937, we get the results as shown in Table X.

TABLE X. COMPARISON OF CLASSICAL AND LOW FLAP SECTIONS

	NUMBER	DEATHS	MORTALITY RATE
Classical sections	945	28	2.96%
Low flap sections	168	5	2.97%

The mortality is practically the same for the low flap and classical sections. It must be remembered, however, that we are comparing series of unequal size (945 against 168), and also the fact that a good many of the low flap cases had longer tests of labor with longer periods of ruptured membranes. We feel that the low flap section, while not infallible, offers a definitely greater margin of safety than the classical route for the case that has had a fairly long test of labor or when the membranes have been ruptured for some time.

Six Porro sections were done in the group of 380 cases. Three were done for multiple fibroids, two for ruptured uterus, and one for contraction ring wrongly diagnosed as ruptured uterus. One mother died, giving a mortality of 16.6 per cent (see Case 2). Three babies were stillborn. Of the 5 mothers that lived, 2 were morbid and 3 nonmorbid.

8. ANESTHESIA

In order to eliminate such factors as duration of labor, length of time membranes have been ruptured, and number of vaginal examinations, only elective cases were studied to determine any possible relationship between type of anesthesia and morbidity.

Table XI shows the percentage of morbidity for each type of anesthetic used.

TABLE XI. RELATION OF TYPE OF ANESTHETIC TO MORBIDITY

	TOTAL	CASES MORBID	PERCENTAGE
General	53	19	35.8%
Spinal	45	14	31.1%
Local	26	7	27.9%

While the percentage of morbid cases is not remarkably lower when done under local infiltration, one gets the definite impression clinically that these cases do much better postoperatively than those done under general or spinal. The patients are more comfortable, they rarely vomit or become distended, they can take fluids by mouth six to eight hours postoperatively, and they usually run a slower pulse than with the other forms of anesthesia.

INSULIN TREATMENT OF DYSMENORRHEA

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MALNUTRITION has long been known as a constitutional reason for dysmenorrhea. Altschul[1] in using insulin for its metabolic stimulating effect in malnutrition found in dysmenorrhea patients an absence of painful menses while under treatment with insulin. He believed that the improvement of the dysmenorrhea with insulin was due indirectly to the resultant improvement in nutrition; so he decided to try the direct effect of insulin on a patient without malnutrition during an attack of dysmenorrhea. He noted relief in ten out of twelve cases. I became interested in this new, easy method of treatment and decided to try it on a few cases. My interest was stimulated by Miller's statement that probably all the glands of internal secretion play their part in the female menstrual cycle and bear a distinct relation also to the nervous and emotional constitution of women, also by the well-known, but frequently forgotten, fact that the sex glands of girls and women are stimulated by the use of insulin.[5, 6]

I have followed a small series of ten cases for five to six months, giving Squibb's regular insulin, five units daily before lunch for three to five days before each menstrual period for two to three months. The girls used in this study were unmarried college students; ages 16 to 29 years, whose menstrual periods were regular and normal in all respects except for the association of pain of varying degrees of severity. Eight out of ten patients (or 80 per cent) were subjectively benefited while under treatment, and three have had several menstrual periods free from pain without the use of insulin. Further observations and more case studies are necessary before we can say whether or not this work has any permanent effects. Table I gives a summary of the case studies to date.

Corroborating Altschul's[2] findings, I have succeeded in relieving the cramplike pains of dysmenorrhea with a single injection of Squibb's regular insulin, 5-7 units given during the attack of dysmenorrhea with a supply of carbohydrate to counteract the antidiabetogenic effect of the insulin.

Altschul and others[2] have suggested that insulin may work through its hypoglycemic effect. Efforts to control the antidiabetogenic effect of insulin and a few blood sugar studies would seem to discredit this hypothesis. The opposite view of this theory, that hypoglycemia is a cause for dysmenorrhea and not a cure, has been taken by Tedstrom and Wilson.[4] The nausea, vomiting and faint feelings associated with dysmenorrhea suggested the hypoglycemia theory. Fasting blood sugar studies showed no uniform variation in fasting blood sugar levels at menstruation as compared with the mid-menstrual level. Eighty per

As far as spinal anesthesia is concerned, about three years ago we had two near-deaths immediately after the spinal injection of neocaine. Since then we have given up its use entirely on service cases and most of us do our private cases under either general or local infiltration anesthesia. We consider spinal anesthesia dangerous for the pregnant woman, as De Lee has been pointing out. We believe local infiltration to be the safest anesthetic for cesarean section as well as the one that gives the patient the most comfortable postoperative course.

9. SUMMARY OF 380 SECTIONS (1932-1937)

Of 11,210 deliveries, 380 were done by cesarean section, an incidence of 3.3 per cent. There were 8 deaths giving a maternal mortality of 2.1 per cent. The number of cases morbid in terms of temperature was 173 or 46.5 per cent. The fetal mortality after correction for nonviability was 3.4 per cent. There were 125 elective sections with one death, giving a maternal mortality of 0.8 per cent for this group. In the elective cases done under local anesthesia the morbidity was somewhat lower than for the cases done under general or spinal anesthesia.

10. SUMMARY OF 1,113 SECTIONS (1907 to 1937)

During this thirty-year period there were 40,388 deliveries of which 1,113 were cesarean sections; an incidence of 1:36 or 2.7 per cent.

Thirty-three mothers died, giving a maternal mortality of 2.9 per cent. The number of cases morbid in terms of temperature was 505 or 45.3 per cent. The corrected fetal mortality for the entire group was 3.5 per cent.

There were 277 elective sections with 4 deaths giving a mortality of 1.4 per cent for this group.

Of the 1,113 cases, 945 were classical sections with a mortality of 2.96 per cent, while 168 were two flap sections with a mortality of 2.97 per cent.

Table XII brings out all the facts mentioned above.

Shelesnyak, M. C., and Rosen, Samuel: Naso-Genital Relationship, Endocrinology 23: 63, 1938.

The periodicity of the estrus cycles of 209 young adult female rats was observed. The effect of treatment of the nasal mucosa with various agents on the estrus cycles was studied in 185 rats with histories of regularity. Control animals received treatment orally. Stimulation with oleum sinapis appeared to affect the regularity of the cycles, chiefly in the follicular phase. Depression effected with tannic and trichloracetic acids produced prolongation of di-estrual phase in 9 of 20 cases. Anesthetization of nasal mucosa with nupercaine produced pseudopregnant state in 58 of 115 cases. Controls which received buccal treatment were negative. Traumatization of the uteri of 16 nupercaine treated animals with prolonged cycles provoked gross decidual growths in 12 cases.

J. THORNWELL WITHERSPOON.

DERMOID CYST OF THE OVARY WITH PERFORATION OF THE URINARY BLADDER AND OF THE SIGMOID

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OVARIAN dermoid cysts have been reported frequently as the cause of peculiar symptoms because of their tendency to perforate adjacent viscera. Our patient is remarkable because of *pilimictio* (passage of hair in the urine) and the passage of feces and gas by urethra.

The patient was a 36-year-old, para i, white married female. She entered Duke University Hospital Oct. 12, 1937. Menarche was at age of fifteen and her periods had been normal and regular. Her family history and past history were irrelevant. She had had urinary frequency for "as long as she could remember."

In July, 1932, when about four months pregnant, her first and only pregnancy, the patient had an attack of cramplike, lower abdominal pain lasting a day. This was diagnosed as kidney colic. No x-rays were taken and no other diagnostic studies were made. She noticed no hematuria or increase in frequency. Two weeks later she had another attack followed by increased frequency and dysuria. She was treated for cystitis throughout the rest of her pregnancy by oral medication and by bladder irrigations. In December, 1932, following a prolonged labor, the patient was delivered by forceps of a full-term healthy child (10.5 pounds). The puerperium was uncomplicated by fever or hemorrhage but "the left side of the patient's body was paralyzed for three months." The lower extremity was particularly affected. She continued to have dysuria and frequency, and following recovery from her palsy, received two cystoscopic treatments for pyelitis. Except for frequency she was fairly well. In July, 1933 she had a severe attack of lower abdominal pain. The pain lasted for about a day and was followed by great abdominal distention and continuous vomiting. During this episode she was febrile, and her abdomen was so tender that she would not allow herself to be examined. She was in bed about a month. Following this she noticed no change in her urinary symptoms and her bowels moved as usual. She had slight lower abdominal pain and would occasionally have a low grade fever. In July and August, 1935 she had attacks of severe lower abdominal pain lasting about two hours. In February, 1936 she had a severe attack of lower abdominal pain lasting almost six weeks, characterized by remissions of a few days' duration. She again vomited continuously and her abdomen was very much distended. She had considerable fever. With this attack she first noticed the passage of gas and feces through her urethra. This was not continuous and was noted only when her bowels "were loose."

On April 6, 1936 she entered Duke University Hospital for the first time. Physical examination was not remarkable except for the pelvic findings. The external genitalia were normal. The perineum was relaxed and lacerated. The cervix was lacerated and chronically infected. The uterus was twice normal size and firm. Catheterized urine specimens were loaded with pus and had a fecal odor. *B. coli communis* was cultured from the urine. A "flat" plate of the abdomen showed "an elongated area of calcification overlying the left margin of the sacrum, possibly in the soft tissues of the pelvis." A cystogram showed marked compression of the upper margin of the bladder, "probably by an enlarged uterus or fibromyoma." Cystoscopy revealed inflammation around the trigone and normal ureteric orifices. Urine from both ureters showed no pus. The diagnosis of chronic cystitis was made and the patient was given bladder irrigations. She was discharged relieved of bladder symptoms on April 15, 1936.

She continued to have marked dysuria and frequency. When seen in the Out-Patient Department on July 7, 1936, the fundus of the uterus was normal in size and no masses were palpable.

TABLE I. CASE STUDIES

	AGE YR.	MENARCHE YR.	DURATION OF SYMPTOMS YR.	ONSET OF PAIN (RELATION TO FLOW)	NUMBER OF INJECTIONS MONTHS	DURATION OF OBSERVATION MONTHS	SUBJECTIVE RESULTS
L. M.	26	11	15	1st day	3	6	Pain relieved
I. R.	16	12	1	1st day	3	6	Pain relieved
H. S.	19	12	4	1st day	3	6	Pain relieved
R. R.	18	12	5	1 day before flow	2	5	Pain relieved
N. M.	25	13	8	1st day	3	3	Relief
A. S.	30	15	10	7 days before flow	2	5	Relief
O. W.	25	11	9	1st day	3	5	Some relief
M. B.	17	11	7	1st day	3	6	Relief
G. W.	20	13	6-7	1st day	3	6	No relief
S. E.	29	13	10	1st day	3	6	No relief

cent of their dysmenorrhea subjects showed a lower blood sugar during menstruation (below 80 mg. per 100 c.c. of blood). These patients were relieved by high carbohydrate feedings and intravenous glucose immediately, but the fact that carbohydrate feeding and intravenous glucose also helped patients with normal or high blood sugars discredits their hypoglycemia theory.

The physiologic explanation of the success of the high carbohydrate feedings and intravenous glucose therapy in the treatment of dysmenorrhea lies in the fact that such therapy may stimulate the pancreas to secrete more insulin, and the favorable results therefore would be due primarily to insulin. This idea is supported by the fact that increasing blood sugar level of patients who had normal or high blood sugars also gave relief. At present, I believe that insulin therapy in functional dysmenorrhea is successful because of its effect on the ovaries. The study of insulin treatment for dysmenorrhea needs further investigation; however the results so far indicate that it is of value in the treatment of this common complaint.

REFERENCES

(1) *Altschul, Alexander:* J. A. M. A. 106: 1380, 1936. (2) Personal communication by Dr. Alexander Altschul, October, 1937. (3) *Novak and Reynolds:* J. A. M. A. 99: 1466, 1932. (4) *Tedstrom and Wilson:* California West. Med. 44: 375, 1936. (5) *Williams, G. A.:* J. A. M. A. 104: 1208, 1935. (6) *Wolf, William:* Endocrinology in Modern Practice, Philadelphia and London, 1937, W. B. Saunders Co.

and to the left of the uterus an ovoid mass about 4.0 by 8.0 cm. was palpable. The right vault was negative. The diagnosis of dermoid cyst of the left ovary with perforation of the bladder was confirmed. A catheterized specimen of urine was loaded with pus and *Staph. aureus* was cultured. Her hemoglobin was 80 per cent (Sahli), red cell count 4,210,000, and white count 6,960. Differential counts were within normal limits. Sedimentation rate was 10.0 mm. in thirty minutes. Her Kahn and Wassermann tests were negative. Cystoscopy showed a tuft of hair about 6.0 cm. long protruding through a fistula on the left side of the fundus of the bladder. The opening appeared about half a centimeter in diameter. A flat x-ray plate of the abdomen showed the calcified area on the left of the pelvis unchanged. Barium enema showed a small irregularity along the lower margin of the sigmoid



Fig. 2.—Barium enema after expulsion. The fistulous tract extends through the calcified area.

and a narrow collection of barium that extended past the calcified area to the region of the bladder. This was considered to have been caused by a small sinus tract extending from the sigmoid.

On Oct. 20, 1937 celiotomy was performed under gas, oxygen, and ether anesthesia. A midline suprapubic incision was made. A knuckle of sigmoid was adherent to a mass of adhesions on the left side of the pelvis. The uterus was obscured by a fold in the bladder which was adherent across the fundus and to both broad ligaments. The right tube and ovary were grossly normal and were adherent lightly to the posterior surface of the broad ligament. The pelvis was carefully isolated by packing and the sigmoid was dissected free. It was adherent to a cystic structure about 4.0 by 8.0 cm. in diameter which was densely adherent to the left anterior region of the bladder. The left ovary was a small cystic structure about 4.5 cm. in diameter and was connected to the cyst only by a few fibrous strands. The sigmoid com-

She reentered Duke University Hospital on Aug. 6, 1936. Nothing remarkable had occurred in the interval. The uterus was found to be slightly enlarged and again no adnexal masses were palpable. The bladder wall felt thick and tender. Her urine was again found to be loaded with pus. Cystoscopy revealed slight trigonitis. She was found to have a residual urine of about 30.0 c.c. X-ray films showed the calcified area in the pelvis unchanged. She was discharged on Aug. 11, 1936 with the diagnosis of chronic cystitis and was given a ketogenic diet.

Dysuria, frequency, and occasional passage of feces and gas through urethra persisted. In May, 1937, she had a sudden attack of massive hematuria lasting three weeks. In June, 1937, she first noticed the passage of hair and small calculi by

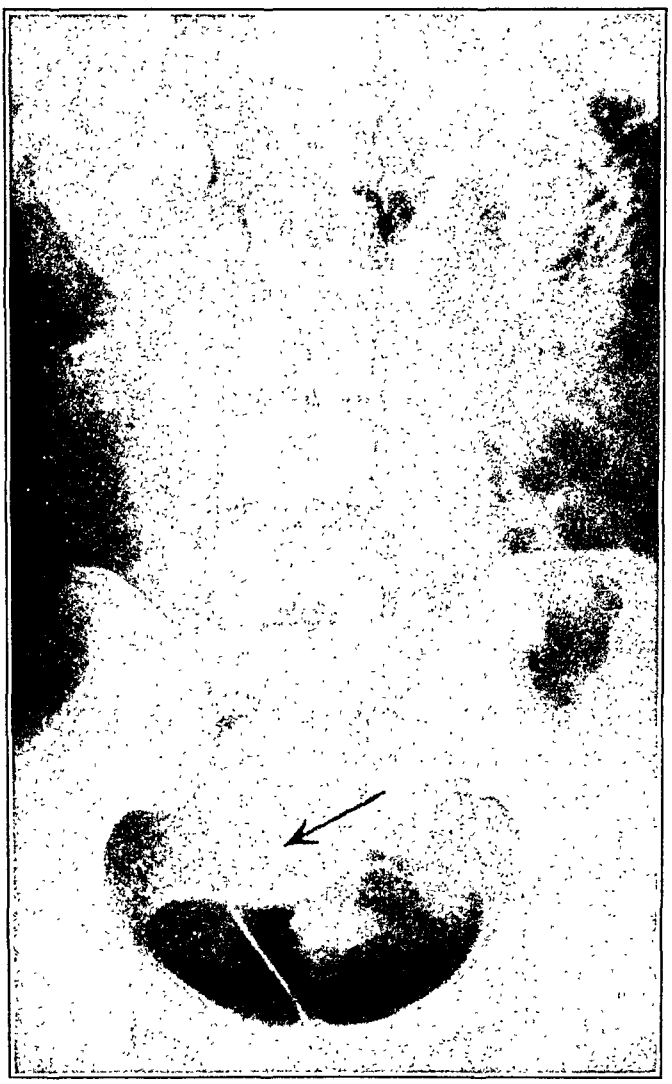


Fig. 1.—Retrograde pyelogram of left kidney. The calcified areas and the deformity of the bladder are visible.

urethra. After the hematuria subsided she was cystoscoped weekly by her local physician. Small masses of hair and stones were removed from her bladder and bladder irrigations were given. In July a tuft of hair was found protruding into the fundus of the bladder and the diagnosis of perforating dermoid cyst was made.

On Oct. 12, 1937 the patient again entered Duke University Hospital. Physical examination showed normal temperature, pulse, respirations, and blood pressure. The only significant findings were slight tenderness and spasm in the left lower quadrant of the abdomen. Pelvic examination showed normal external genitalia, relaxed and lacerated perineum, small cystocele, and small rectocele. The cervix was lacerated and eroded. The fundus was normal size, anterior, and movable. Anterior

of malignancy in the dermoid. Stratified epithelium and numerous glandular structures were present. There were some brain tissue, much bone and cartilage and one area that showed a collection of renal tubules. The smaller structure proved to be a simple cyst with a fibrous wall and an endothelial lining."

The patient returned to the dispensary three months after the operation. She was completely relieved and had gained weight. Cystoscopy revealed a small reddened plaque at the site of the urinary fistula. Her urine was entirely normal.

The above patient is interesting because of the accuracy with which her symptoms can be interpreted in retrospect. The dermoid obviously had its origin in the left ovary. During her pregnancy in July, 1932 the initial attack of pain was probably due to torsion of the pedicle. The "paralysis" post partum was apparently due to some cause totally unrelated to her pelvis, as the size and the anterior position of the cyst would have prevented any pressure on the lumbosacral plexus. The at-



Fig. 4.—Posterior view of the dermoid after removal.

tack of fever, distention, vomiting, and abdominal pain in July, 1933 was undoubtedly due to peritoneal irritation. At that time the dermoid was probably completely separate from the ovary. The attack was caused either by infection in the cyst or leakage of some of the contents with the production of a sterile peritonitis. Feces and gas appeared in the urine in February, 1936, and at that time the dermoid was probably receiving its blood supply entirely from the sigmoid and bladder. The mass felt in April, 1936 may have been due to the accumulation of feces in the cyst or to incomplete evacuation of the contents. The mass disappeared in August, 1936 because of escape of the cyst's contents and the collapse of its fibrous walls with the better establishment of the fecal fistula. The mass palpable on her last admission was due to enlargement of the subsidiary locules.

Ewing[22] has stated, "The dermoid may migrate from the ovary and become implanted elsewhere or perforate the hollow viscera." The etiologic factor in the formation of fistulas appears to have been primarily interference with the blood supply of the dermoid and subsequent infection of its contents. In none of the cases reported was malignancy a factor.

municated with the cyst through a fistula about 0.5 cm. in diameter. The defect in the sigmoid was closed with a double layer of inverting sutures. The bladder was then freed, and the dermoid cyst excised from its attachment to the bladder. The fistulous tract communicated through the dermoid and a tuft of hair about 6.0 cm. long, lightly encrusted with calcareous material, was pulled out of the bladder as the cyst was removed. The opening in the bladder was slightly enlarged and infolded with a double layer of continuous sutures. The remnant of the left ovary was excised and the abdomen drained by posterior colpotomy.

An inlying catheter was left in the bladder for nine days, and she was given 0.25 per cent acetic acid bladder irrigations every two hours. A rectal tube was left in place most of the time for the first five days, since no cecostomy had been performed. For three days postoperatively the patient was given nothing by mouth

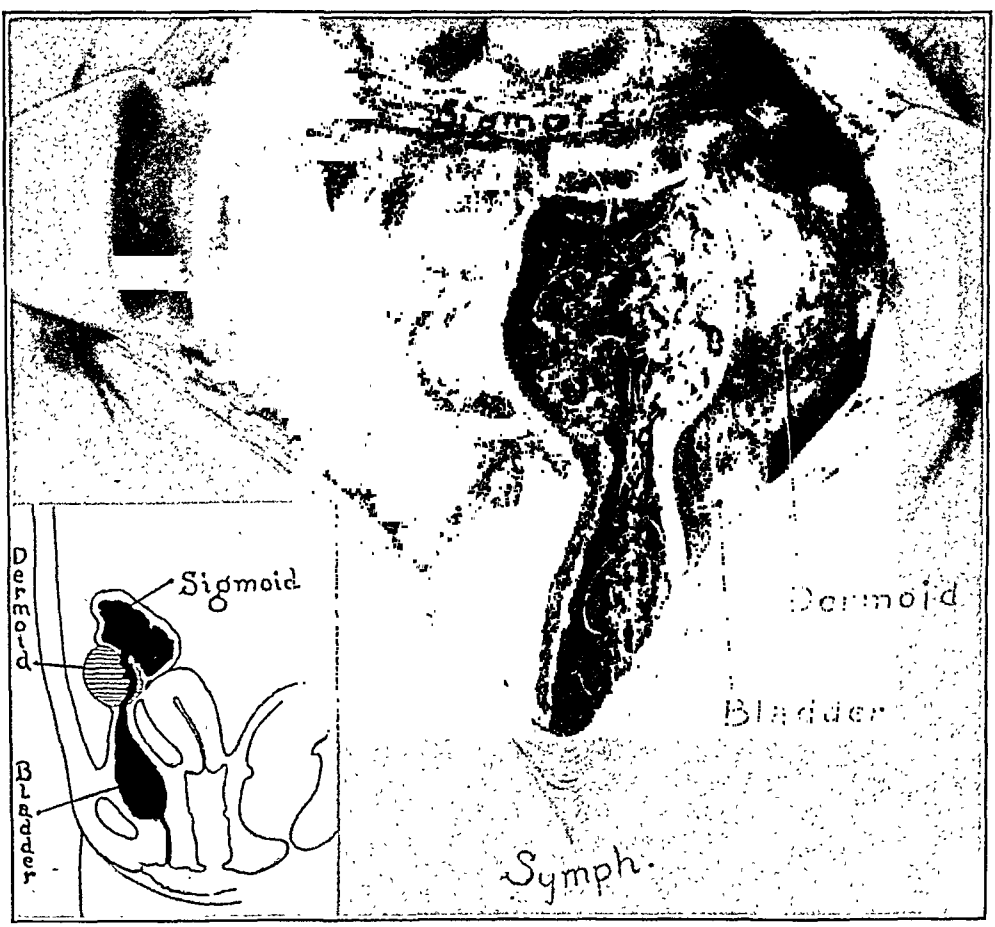


Fig. 3.—Diagram of the findings at operation.

and received parenteral fluids. Her temperature and pulse dropped to normal and she was given liquids by mouth. She passed much flatus by rectal tube. The abdominal wound healed by first intention. Vaginal drains were removed on the seventh day. This was followed by the drainage of considerable amounts of foul pus from the vagina. On the eighth postoperative day the patient developed a small perianal abscess. It was incised under gas-oxygen anesthesia on the tenth postoperative day. Her bowels thereafter moved spontaneously with mineral oil. She was discharged on the eighteenth postoperative day completely relieved of her symptoms.

The pathologic report was as follows: "The specimens were a large dermoid cyst and a smaller cystic structure. The dermoid was 2.0 by 4.0 by 8.0 cm. and was bilocular. Between the lobes was a groove containing hair and feces. On section the locules contained clear fluid and there was much calcium in their walls. There were some papillomatous outgrowths in the lining. The smaller cyst was 4.5 cm. in diameter, unilocular and had a smooth lining. Microscopically there was no evidence

NEPHRECTOMY FOR UNILATERAL TUBERCULOSIS FOLLOWED BY PYELITIS IN THE REMAINING KIDNEY DURING PREGNANCY*

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NEPHRECTOMY for unilateral tuberculosis followed by a pyelitis in the remaining kidney during pregnancy has not been reported before. Nephrectomy during pregnancy for all types of kidney pathology is uncommon; nephrectomy for tuberculosis during pregnancy is rare. Stevens[1] in 1924 published a collected series of 18 cases including 2 of his own. Since that report 5 cases were reported by Pugh,[2] Ravina[3] reported 3 cases, and Andrè[4] reported 1 case.

The essential symptom complex is not typical. The right kidney is more frequently involved than the left. In the cases reported the disease has been diagnosed from the second to the eighth month of pregnancy. The onset has been insidious in most cases. There has been usually frequency of urination and nocturia. Dysuria has been a variable complaint. Gross pyuria may be present especially if there is a secondary infection; on the other hand the urine is frequently clear with no albumin or only a faint trace showing. Hematuria occurs frequently and early, often pointing the way to the diagnosis. The physical signs were often inconspicuous; the majority of cases were afebrile and had mild to moderate costovertebral tenderness. In some cases there was suprapubic tenderness. Urinalysis was not always helpful. The incidence of positive smears for the tuberculosis bacillus in the urine varied with different investigators from 25 per cent to 100 per cent. Invaluable and often the sole diagnostic aid have been cystoscopy and intravenous urography. Both these procedures have been important in ruling out other kidney nephropathies, such as calculus, pyonephrosis, and tumors.

In evaluating the results of treatment by other investigators, statistics show nephrectomy is the procedure of choice for unilateral *surgical* tuberculosis. In the 18 cases reported up to 1924, 12 patients had nephrectomies and they all recovered. In 5 nonoperated cases 3 had acute exacerbations, 1 died in the eighth month, and in 1 no noticeable change was noted. In the operated group 6 living children were delivered at term; 2 patients aborted, 1 miscarried two months after operation, and 1 delivered a premature dead fetus at seven months, four months after her nephrectomy. The outcome of the pregnancy was not mentioned in 2 cases. In the 5 nonoperated cases 2 patients aborted; 1 infant was infected at birth and died of tuberculous meningitis eight months later; the fourth case delivered a living normal child at term. The result in the fifth case was not mentioned.

Pugh in 1936 reported 5 cases of nephrectomy for unilateral tuberculosis, the largest individual series, with no maternal or fetal mortality. Ravina in 1931 reported 3 cases; in 2 the mother and child recovered. The third patient was operated upon postpartum but died on the eighth day postoperative. Andrè's patient was operated upon in the third month; the patient had a premature labor four months later.

When one considers the comparative results obtained in the operated and nonoperated cases cited above; when one realizes that the mortality for the mother in kidney surgery, quoting Mussey,[5] is no greater than the same type of surgery in nongravid women; then it is our opinion that pregnancy offers no contraindication for nephrectomy in cases of advanced unilateral kidney tuberculosis.

Most authorities agree that future pregnancies should be discouraged, but if the mother is insistent consent should not be given, quoting Matthews,[6] Stevens, and Schmidt,[7] until the patient has been symptom-free for from two to three years.

*Presented to the Section of Obstetrics and Gynecology at the Academy of Medicine, December 28, 1937.

Haggard[11] in 1907 reported the case of a woman in which a right-sided dermoid had ulcerated into the cecum and bladder. Derveaux[15] in 1909 reported a patient in whom a dermoid had involved both the rectum and bladder. He marsupialized the cyst and allowed the fistulas to close spontaneously. Thomas and Exley[26] in 1930 reported a patient with a dermoid cyst opening into the bladder, an appendiceal abscess, the ileum and sigmoid. According to Szathmary,[30] Mayeda and Slimgava's patient had a dermoid communicating with a loop of small bowel and the bladder. No other patients in whom both bladder and bowel were involved by perforating dermoids appear to have been reported. More numerous references are available to dermoids that have involved a single viscus, including even the gallbladder, the abdominal wall, peritoneal cavity and vagina.

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Cella, C., and Georgescu, I. D.: Experimental Studies of the Physiology and Pharmaco-Dynamics of the Uterine Tube, Arch. f. Gynäk. 165: 36, 1937.

The uterine tube shows automatic contractions and actual peristalsis when removed. Such automatic contractions are demonstrable in every portion of the tube. This peristalsis is produced by both the circular and the longitudinal muscle fibers. The peristaltic rhythm varies between 2 and 6 per minute, begins at the ampulla and passes down to the cornual end. The stimuli for these peristaltic contractions arise in the muscle fibers of the tube as well as in the ganglion cells.

There are only minimal contractions during menstruation; they are most pronounced at the time of ovulation.

These isolated tubes respond to temperature, pH concentration, medications, hormones and bacterial products. The optimum temperature is 37.5 to 38° C. Lower temperatures inhibit and increased temperatures increase peristaltic activity. The optimal pH is 7.4. Barium chloride increases peristalsis to the point of tetany. Ethyl alcohol stimulates in small doses and inhibits in large doses. Lipiodol, alkaloids such as nicotine, adrenalin, ergot, pilocarpine and eserine increase peristalsis. Large doses of alkaloids, atropine, papaverine, etc., decrease peristalsis. Estrin and corpus luteum hormones slightly stimulate peristalsis. Prolan has no direct effect but sensitizes the tube to the action of estrin.

RALPH A. REIS.

ureteral catheter at ½ cm. from the ureteral orifice. When pressure was exerted on the right kidney, there was bleeding and a ribbon of pus resembling tooth paste expressed into the bladder.

Intravenous pyelogram (Fig. 1) revealed a normally functioning left kidney with slight generalized dilatation of the ureter and pelvis of the kidney. There was some blunting of the calyces. The right side showed an irregular shadow, which was also present on the flat plate, and was interpreted as inspissated pus. This shadow did not show up in the reproduction (Fig. 1). Catheterized specimen of urine from the bladder was negative for the tuberculosis bacillus; the specimen from the left kidney cultured *B. coli*. The diagnosis of the genito-urinary consultant was "nonfunctioning pyonephrotic right kidney with stricture of the lower right ureter, quite likely tuberculous in origin."

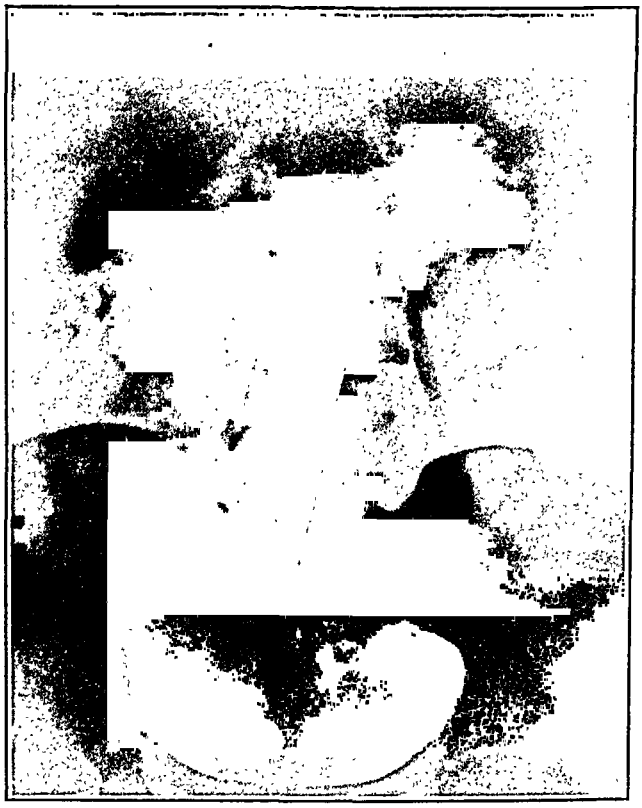


Fig. 2.—Intravenous pyelogram ten days post partum. Left kidney normal except for some enlargement in transverse diameter. Some blunting of the calyces and moderate dilatation of the left ureter. Bladder filled normally.

Consequent preoperative, voided specimens of urine were negative for tuberculosis, except for one specimen which showed an isolated acid-fast bacillus. At the time this one finding, we believed, could not be accepted as positive evidence of the tuberculous origin.

Nine days after admission, under gas-oxygen-ether anesthesia a right nephrectomy was done by Dr. Wilhelm of the genito-urinary service. About 10.5 cm. of the right ureter was removed. The right kidney was greatly enlarged and distended. The cortex was completely atrophic, only a cystic membrane remained. The ureter was thickened and indurated.

The essence of the microscopic report of our pathologist Dr. Plaut was as follows: "There are many tubercle-like formations and giant cells at the inside of the distended calyces. The giant cells for the most part resemble the foreign body type and often are situated in the neighborhood of spaces whose shape is suggestive of fatty acid crystals. The centers of many of the tubercle-like formations contain leucocytes. Extensive search for tuberculosis bacilli was negative."

CASE REPORT

The patient was a 26-year-old white multipara, gravida ii, para i who attended our ante-partum clinic on April 7, 1937. The family and past history were negative. Menses never showed any aberrations. The last menstrual period was Nov. 7, 1936. The expected date of labor was Aug. 14, 1937. Her previous pregnancy three years ago was normal; the child is now living and well. The patient was five and one-half months pregnant at the first examination. Except for a systolic murmur heard at the apex with no evidence of decompensation the physical examination was negative. The Wassermann was negative. The blood pressure was 100/60. The weight was 148 pounds. Urine examination was reported negative except for a faint trace of albumin. In the next 4 visits to our clinic there was a faint trace of albumin in the urine reported on 2 occasions and on the 2 other occasions were reported as completely negative. The patient had no complaints during this period and no



Fig. 1.—Intravenous pyelogram showing a seven months pregnancy. Function of the left kidney was normal. The right side showed no function.

abnormal findings were noted until seven weeks after registration when she was admitted to Beth Israel Hospital with the following complaints:

1. Hematuria.
2. Pain—dull in character, in the right lumbar region and suprapubically.
3. Frequency and nocturia.

} All of 2 days *duration.*

Physical examination on admission was essentially negative. Temperature was normal. Blood pressure was 126/80. There was no costovertebral or abdominal tenderness present, no kidney masses were palpable. X-ray of the chest was negative. Laboratory data: R.B.C., 3,000,000; Hg., 68 per cent. Blood chemistry was normal.

The first clue as to the essential pathology was disclosed by cystoscopy. The bladder was normal. The left ureteral orifice, ureter, and kidney were normal. The right ureteral orifice showed a bullous edema, biopsy of this tissue subsequently was reported as inflamed tissue. There was an impassable obstruction to the

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THE EFFECT OF IRRADIATION ON THE FUNCTION OF THE OVARY IN YOUNG GIRLS

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NOT infrequently there is a hesitancy to employ irradiation as treatment for gynecologic or other conditions near the ovaries in young women because of the quite general but mistaken belief that such therapy inevitably produces a permanent sterilizing effect. Especially is this the case when irradiation is requested for girls under the age of puberty.

It cannot be denied that there would appear to be some reason for such a supposition. In the early days of x-ray therapy, Halberstaedter[1] was first to note the special sensitiveness of ovarian tissues to these rays, and later Bergonie and Tribondeay[2] enunciated the axiom that the more embryonic the tissue the more sensitive it is to irradiation, so that it was not illogical to expect that the ovaries of young girls would be especially sensitive to irradiation.

Although experience has taught that the younger the woman the more responsive to irradiation when employed in suppressing menstrual function, yet it has been noted likewise that the younger the woman treated, the greater the likelihood of reparation and restoration of function and the less probable permanent sterilization.[3]

As for permanent injury to the ovum contained in the ovary, it is our opinion that the immature graafian follicles, while likely to be affected by irradiation because of their embryonal character, may later recuperate sufficiently to mature, become fertilized and produce normal children. This has occurred in cases where moderate irradiation is employed and in young females where sterilization has been only temporary, so that subsequent menstruations have been followed by normal production of ovum which were capable of fertilization resulted in the development and birth of a normal, healthy baby.[4]

The case herewith presented referred to me by Dr. Pol N. Coryllos, is an example of intensive irradiation administered for pelvic tumor, to a girl 4 years old with both x-ray and radium therapy directed through the pelvis over a long period of time. Treatment was given when the patient was but four years of age and at present she is 14 years old and has been menstruating normally for twenty-one months, menstruation having begun at 12 years of age.

Provisional Pathologic Diagnosis.—Infected hydronephrosis with foreign body inflammation. No evidence of tuberculosis.

The patient's postoperative course was smooth and uneventful. She was discharged to the prenatal clinic on the fifteenth postoperative day with the wound completely healed except for a small sinus at the site of the drainage tract.

One month later the patient was re-admitted acutely ill with a temperature of 102.6° F. She was suffering with chills and fever, dysuria, frequency, and left lumbar pain for two days. Physical examination revealed left lumbar tenderness with no mass palpable. The uterus was about the size of an eight months' pregnancy. The fetal heart was in the R.L.Q.; the rate was 130 per minute. The position was R.O.A.

Cystoscopy at this time revealed the following: the bladder and the left ureteral orifice were inflamed. The left ureter was catheterized for 14 cm. where an impassable obstruction was met. Following the removal of the catheter a rapid flow of concentrated, blood-tinged urine followed. Indigo-carmine in good concentration appeared in fifteen minutes. Culture of the specimen revealed *B. mucosus capsulatus;* no acid fast organisms were found. The diagnosis was pyelitis. One hour after



Fig. 3.—Left kidney visualized, slightly enlarged but normal in shape and position. Pelvis, kidney calyces, ureter, and bladder filled well. Function was excellent.

cystoscopy the patient's membranes ruptured spontaneously and she went into labor, delivering in three hours a normal, male infant, weighing 7 pounds 3 ounces. In forty-eight hours the temperature was normal. The urine was clear in nine days on urotropin and acid sodium phosphate. She was discharged after an uneventful postpartum course on the thirteenth day.

Nine weeks later, the patient was re-admitted to the hospital for the treatment of 2 pin-point discharging sinuses at the site of the nephrectomy wound. She had no complaints. At this time a third intravenous pyelographic study was done.

This last plate illustrates strikingly how well the kidney and ureter recovered from the double burden of pregnancy and infection.

Although many urine specimens had been examined during the first and second admissions, only 1 specimen had shown an isolated acid-fast bacillus. During her third admission, five months after the beginning of her illness, a twenty-four-hour specimen of urine revealed positive evidence of the tubercle bacillus.

permanent. Normal menstrual periods can occur at puberty and proceed regularly thereafter in young women previously treated by x-ray therapy.

NOTE: A personal communication from Dr. Geo. L. Streeter, Director of the Carnegie Institute Department of Embryology, contains the following suggestion:

"I believe the factor involved in your case is the principle that the more primordial the cells the more resistant they are to x-rays, whereas, ova in the later stages of their differentiation are easily destroyed by x-ray and the primordial cells which will produce their successors are perhaps not so easily affected. In your case the heavy treatment that the patient received certainly killed off all the follicles but in the course of time the primordial ovarian tissue produced a new crop of eggs along with their accessory cells and this finally resulted in the resumption of menstruation."

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55 EAST 86TH STREET

Klaften: Treatment of Pruritus Vulvae and Certain Forms of Dermatitis, Zentralbl. f. Gynäk. 61: 972, 1937.

During the last three years Klaften treated 38 women with intractable pruritus vulvae with estrogenic hormone. Most of them had previously been treated in various ways, some even with roentgen rays. The youngest patient was 30 and the oldest 82. At first the author administered estrogenic substance hypodermically and by mouth but later resorted to percutaneous inunction of the estrin locally. For the latter procedure, seven times the hypodermic dose is necessary to accomplish the same results. A salve is prepared and a sufficient amount of it rubbed into the skin locally so that 4,000 units are applied daily. As improvement becomes evident, the treatments are given every second day and then with lessened frequency. The patient should be warned that at the beginnnig of the treatment there is often an increase in itching for a while, just as with intramuscular use of estrin. In some cases the author combined hypodermic administration with percutaneous application of estrin. He employs estrin treatment for other dermatatides due to ovarian hypofunction.

The hormone treatment of pruritus vulvae cured 25 of the 38 patients (65.7 per cent) for 6 to 30 months. In 4 cases (10.5 per cent) there were recurrences 9 to 21 months later, but a new course of estrin treatment brought about cure.

In many cases the breasts became enlarged, and in women past the menopause occasionally uterine bleeding was started. The author encountered some women who could not tolerate estrogenic substance; swelling of the extremities, face, hands, vulva and anal regions and a generalized pruritus developed. These symptoms can be avoided by using the estrogenic substance percutaneously.

Excellent results were obtained in women with ovarian hypofunction but not in women with normal ovarian function. The latter had severe reactions following both hypodermic and local applications, and the treatment had to be stopped. Likewise, women with a three-week cycle were not helped by estrogenic substance. The author warns against the use of radiation therapy in women within the menstruating age, especially since this form of treatment does not benefit them. For these patients he advises foreign protein injections.

J. P. GREENHILL.

CASE HISTORY

H. P., aged 4 years, was referred for treatment April 5, 1928, for a large tumor of the pelvis situated over the coccyx area, palpable through the abdominal wall and the rectum. The mass almost completely occluded the rectal canal and the small examining finger could not be passed beyond it. The x-ray showed a large dense mass in the pelvis seemingly attached to the coccyx. From May, 1928, until July, 1928, she received high voltage x-ray therapy through the anterior and posterior pelvis, receiving a dose of 1200 r. (measured in air) (in today's measurement). In November, 1928, a radium applicator was inserted in the rectum and a dose of 990 mg. hours given. In January, 1929, the patient was examined and the mass was still unchanged although there was a definite relief of rectal blockage. Further x-ray therapy was advised and during January, 500 r. (measured in air) was given. The patient returned again in April, 1929, and the mass was somewhat smaller. Additional x-ray therapy of 400 r. (measured in air) was given through the pelvis.



Fig. 1.—Patient at four and fourteen years of age.

The patient was seen again in January, 1930. The mass though smaller but still being palpable, 600 r. (measured in air) of x-ray therapy was administered. Until May, 1931, the patient did not report for observation. At that time, she was 7 years old and the mother thought the mass had grown. Examination did not reveal any increase in size of the tumor mass, but because it was still palpable additional x-ray therapy was given, 600 r. (measured in air) being administered.

She was seen again by us on Sept. 11, 1936, her weight was 122 pounds, the mass was slightly palpable, but she had no difficulty with bowel movement. Her menstruation began without difficulty March 27, 1936, when she was 12 years old and has continued in a normal manner since.

The patient was examined on Sept. 9, 1938, by Dr. Coryllos who reports her in excellent condition, no mass being palpable at the site of the former involvement, and the patient had continued to have normal menstrual periods.

CONCLUSIONS

X-ray therapy is not necessarily destructive to ovarian tissues. The younger the patient the less probable is sterilization by irradiation to be

and acute dermatitis of the external genitalia and the femoral regions may result. This dermatitis usually starts when the mycelia invade the skin of the irritated areas and form pustules. These break and spread the infection over a larger area until the final picture presents deeply encrusted regions with an increased number of pustules. Diagnosis may also be made by microscopic examination or culture of material obtained from these pustules.

In the older chronic cases of moniliasis, no discharge or caseous patches are present, but the vagina may present a dry, encrusted appearance.[4] These cases may also be diagnosed by the method described above. Moniliasis differs from trichomoniasis in that the infection, if it does not reach the dermatitis stage, is self-limiting, while trichomonas infections increase in severity unless treated.

TREATMENT

Moniliasis will respond to treatment with many common antiseptics such as 2 per cent aqueous solution of gentian violet. In our study silver picrate was found to be as effective as gentian violet, without the disadvantage of the intense staining. After a positive diagnosis has been made, the vagina is cleansed with a cotton sponge saturated with a suspension of kaolin in aluminum hydroxide.* The vagina is then rinsed with sterile water and dried. This procedure removes the debris and mucus present in the vagina and on the cervix which might protect the tissue from the medicament.

If a plug of mucus is present in the cervical canal or external os, it must be removed because it may serve as a site for reinfection. The removal of this mucus sometimes causes slight vaginal or cervical bleeding, due to the removal of the mycelia from the vaginal mucosa and the cervical glands and tissue.

The next step in the treatment is to paint the vagina with a 1 per cent aqueous solution of silver picrate. Then 5 gm. of 1 per cent silver picrate in kaolin are insufflated into the vagina by means of a vaginal powder insufflator. This constitutes the initial treatment, which is repeated at weekly intervals, or oftener, as required. In the more severe cases in which the vagina was dry, powder insufflation was not used since this further drying proved more irritating. The treatment of such cases is limited to painting the vaginal tract with a 1 per cent aqueous solution of silver picrate.

RESULTS

As shown in the table, 19 cases (Cases 1, 3, 5, 6, 7, 8, 10, 11, 13, 15, 16, 17, 19, 20, 21, 24, 25, 27, and 28) were found positive by smear and culture for monilia. All had a vaginal discharge. They were negative for *Trichomonas vaginalis* and no dermatitis was present. Two cases (Cases 12 and 18) doubtful on smear, proved to be positive on culture, neither one presenting a dermatitis. One case (Case 18), however, showed *Trichomonas vaginalis*. Two cases (Cases 19 and 14) were positive

*Preparations supplied through the courtesy of John Wyeth & Brother, Incorporated, Philadelphia.

also claim that the same 20 per cent should be treated.[4] *Monilia albicans* may be found associated with *Neisseria gonorrheae* in rare instances, but more commonly associated with *Trichomonas vaginalis.* Therefore, the growth of *Monilia albicans,* favored by an acid media, is enhanced in the normal vagina, containing a preponderance of Döderlein's bacilli and maintaining a pH of from 4.0 to 4.6.

CONCLUSIONS

1. A satisfactory method for diagnosis both microscopic and cultural is presented, together with the clinical appearance of moniliasis of the vaginal tract.

2. Silver picrate is shown to be a satisfactory form of treatment for vaginal moniliasis.

The authors wish to express their appreciation to Dr. D. H. Wenrich, Professor of Zoology at the University of Pennsylvania, and to Dr. J. H. Clark, Director of the Pathological Laboratories, Philadelphia General Hospital.

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AN UNUSUAL IRREGULARITY OF THE FETAL HEART DURING PREGNANCY

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MARKED irregularities of the fetal heart are usually associated with some condition detrimental to the life or health of the fetus. Bradycardia or premature contractions with a murmur have made possible the diagnosis of congenital heart disease before birth.[1] Marked arrhythmias suggestive of auricular fibrillation have been noticed in association with abortion or premature labor.[2] Holterman[3, 4] has noted premature contractions as an early sign of threatened fetal death in protracted gestation and reports a case in which the baby died before a cesarean section could be performed, along with two other cases in which healthy babies were obtained by cesarean section. Premature contractions during pregnancy have been considered to be due to hydramnion.[5]

The following case is an exception to the general rule, a marked arrhythmia of the fetal heart being present without any apparent abnormality of the fetus.

Mrs. J. K., aged 33, white housewife, one pregnancy six years previously, the history of which showed nothing unusual. Her past and family histories were essentially negative.

When first seen when about five months pregnant, examination showed a healthy woman with the uterine fundus one fingerbreadth below the umbilicus and a faint but regular fetal heart in the midline, rate 140. Shortly afterward she fell and fractured the left fibula for which she wore a plaster splint for one week. The fetal heart was next examined at about six months and again was 140 and regular. However, at the seventh month a decided irregularity was found and was noted thereafter at each one of the nine subsequent prenatal visits. This irregularity showed many variations but usually resembled premature contractions. Sometimes the regu-

for monilia on smear and culture, although the vagina was dry and a severe dermatitis was present on the inner aspect of the thighs. No trichomonas or discharge was present. In one case (Case 4) a positive smear and culture were obtained. There were no trichomonads present, but there were a vaginal discharge and a slight dermatitis. In Case 22 smear and culture were both positive although the vagina was dry and crusted, and no trichomonads, discharge, or dermatitis was recorded. Case 23, a girl aged 15 years, presented the most marked symptoms and was treated for a longer period of time than any of the others. This case gave a positive smear and culture for monilia and trichomonas in the presence of a profuse discharge and a severe dermatitis. Case 26 yielded a negative smear and positive culture for monilia in the presence of a discharge and slight dermatitis, although no trichomonads were demonstrable. Case 2 showed a positive smear and culture for monilia. Trichomonads and a severe discharge were present, but there was no dermatitis apparent.

Two patients (Cases 8 and 17) were cured of their infection after receiving one treatment. Fourteen patients (Cases 1, 2, 5, 6, 7, 11, 12, 13, 16, 20, 21, 24, 26, and 28) responded to two treatments each and remained free from symptoms for the three months following treatment during which they were observed. Five patients (Cases 3, 10, 15, 19 and 27) responded to three treatments and remained negative by smear and culture for the same period of time; 5 patients (Cases 4, 9, 14, 18, and 25) responded to four treatments. Cases 22 and 23 required five and eight treatments, respectively. All patients were followed for three months after the cessation of treatment and were found to be negative by both smear and culture at the end of that time.

TABLE I

CASE	AGE	MONILIA ALBICANS		TRICHOMONAS VAGINALIS	DISCHARGE	DRY	DERMATITIS	NUMBER OF TREATMENTS
		SMEAR	CULTURE					
1	29	+	+	−	+	−	−	2
2	32	+	+	+	+	−	−	2
3	38	+	+	−	+	−	−	3
4	22	+	+	−	+	−	+	4
5	23	+	+	−	+	−	−	2
6	28	+	+	−	+	−	−	2
7	52	+	+	−	+	−	−	2
8	21	+	+	−	+	−	−	1
9	31	+	+	−	−	+	+	4
10	56	+	+	−	+	−	−	3
11	18	+	+	−	+	−	−	2
12	28	?	+	−	+	−	−	2
13	40	+	+	−	+	−	−	2
14	23	+	+	−	−	+	+	4
15	36	+	+	−	+	−	−	3
16	27	+	+	−	+	−	−	2
17	31	+	+	−	+	−	−	1
18	33	?	+	+	+	−	−	4
19	25	+	+	−	+	·	+	3
20	19	+	+	−	+	−	−	2
21	25	+	+	−	+	−	−	2
22	41	+	+	−	−	+	−	5
23	15	+	+	+	+	−	+	8
24	24	+	+	−	+	−	−	2
25	16	+	+	−	+	−	−	4
26	48	−	+	−	+	−	+	2
27	25	+	+	−	+	−	−	3
28	36	+	+	−	+	−	−	2

DISCUSSION

Several workers claim that about 20 per cent of the patients harboring *Monilia albicans* do not present clinical symptoms, although they

DICEPHALOUS MONSTER

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Although this type of monster is not rare, it is uncommon enough to deserve reporting, mainly because it was delivered spontaneously.

The patient was delivered in one of the outlying towns of Little Rock and was sent in to the medical school. A midwife was the only one in attendance and she

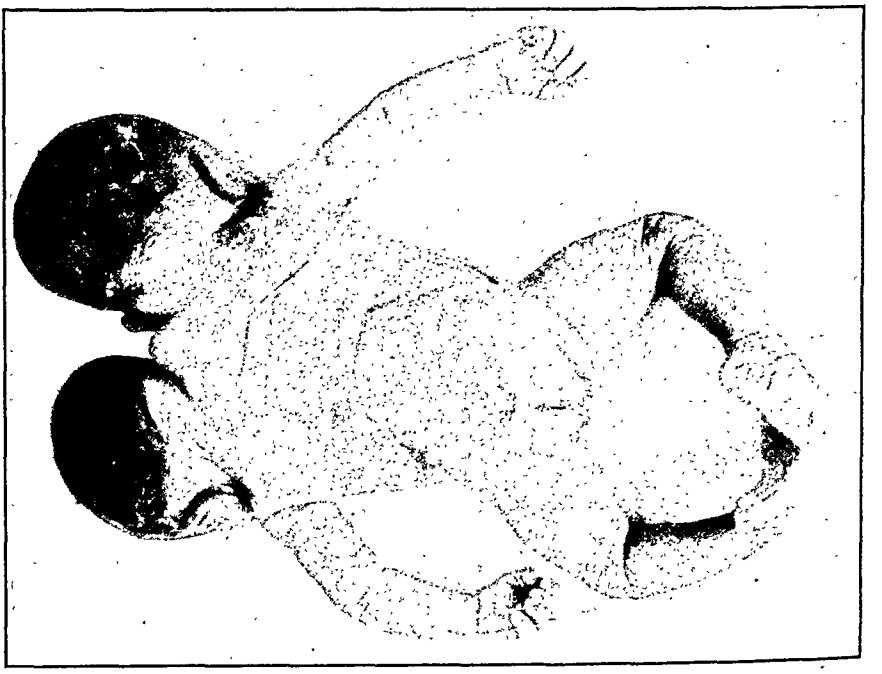


Fig. 1.—Posterior view of the monster.

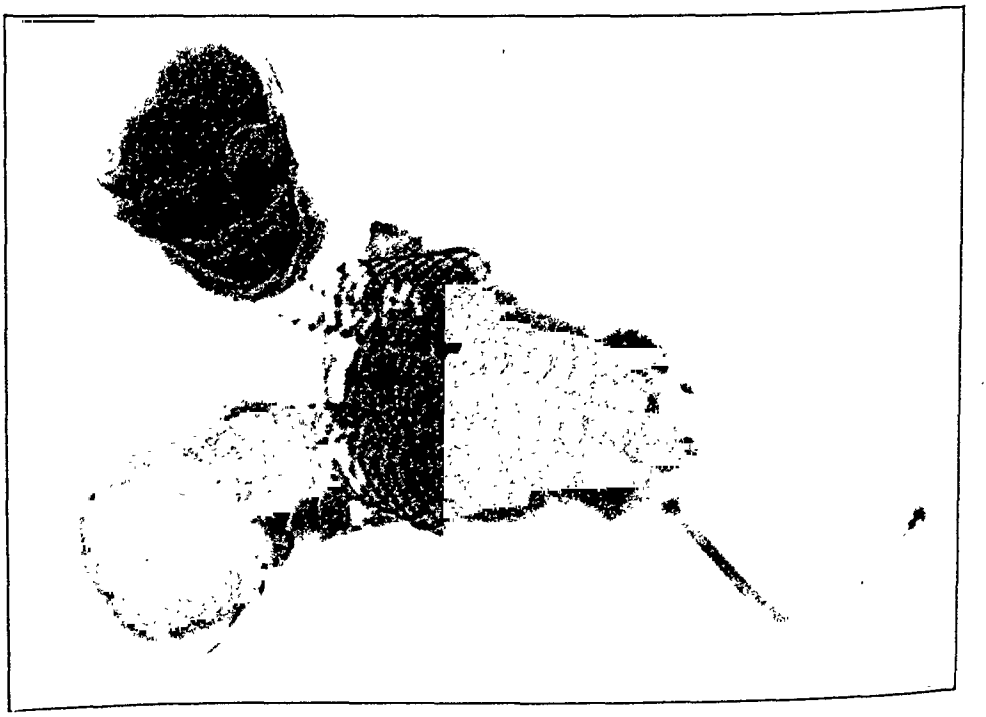


Fig. 2.—X-ray picture showing skeleton formation of the specimen.

lar rhythm was interrupted by a premature contraction every third or fifth beat. Sometimes the premature contraction occurred every second beat for runs of 10 or 100 or more beats. Occasionally there seemed to be nothing but a jumble of sounds. There were no murmurs heard at any time.

An attempt was made to take an electrocardiogram of the fetal heart with leads from the abdomen but a nearby power transformer upset the electrocardiograph just as preparations were completed, although there had been no interference while the mother's tracing was being taken.

As to what prognosis to give the patient we were in doubt. However we did give her a guardedly good prognosis, likening the case to the idiopathic premature contractions of adult life.

The condition continued throughout an uneventful nine hour labor and for six days thereafter. An electrocardiogram taken on the first day after birth proved the nature of the arrhythmia and showed the premature contractions to be ventricular in origin. Repeated examinations after the sixth day and in the next year of life revealed a regular rhythm at all times.

Two hours after delivery the nurse was disturbed by an irregularity of the mother's pulse and then for the first time the mother's heart beat showed premature contractions. These also proved to be ventricular. They continued all during her twelve day stay in the hospital and for at least three and one-half months postpartum, disappearing during exercise only to appear again when the heart slowed down. The patient drank only one cup of coffee and smoked only four or five cigarettes a day. Quinidine sulphate and phenobarbital were given without benefit. As there were no symptoms the medications were discontinued and in the course of another four months the arrhythmia stopped.

This condition is probably not as rare as it would seem, for Hyman[2] in 1930 reported six cases of fetal premature contractions which were demonstrated by use of the phonocardiograph, an instrument which records the fetal heart sounds. In each of these cases healthy babies were born and the arrhythmia disappeared within a few days after birth, the longest lasting about eight days. Somewhat similar cases have also been reported by Lork[6] and by Rihl and Weinzier.[7]

The continuous auscultation of the fetal heart by means of an amplifying stethoscope as recently described by Matthews,[8] and increasing use of fetal electrocardiography will no doubt add much to the study of fetal arrhythmias.

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Kreis, J.: Treatment of a Primary Ulcer of the Vagina After the Menopause With Folliculin, Bull. Soc. d'obst. et de gynéc. 27: 334, 1938.

The author found in a 64-year-old woman a bloody vaginal discharge coming from an ulcerated area. Biopsy revealed a total absence of epithelium. For six months he cauterized the ulcer but failed to cure it. Then he gave a few injections of estrin and prescribed some by mouth. Bleeding ceased and the ulcer disappeared. Two years have elapsed and there has been no return of the ulcer. Most likely the estrin produced epithelization of the ulcerated area.

J. P. Greenhill.

fingers well up towards the palm of the right hand, throw it across the left arm as shown in Fig. 1 with the right hand palm down.

Now turn the right hand over, palm up, so that the two strands of gauze are crossed as shown in Fig. 2.

Next, while preserving the twist in the loop of gauze, move the right hand towards the left arm and place the thumb distal to the distal leg of the original loop, with the fingers around which the loop of gauze is held placed medial to the distal leg of the loop (Fig. 3). Now simply bring the fingers and thumb together around this strand of gauze and pick it up, turning the right hand palm up (Fig. 4).

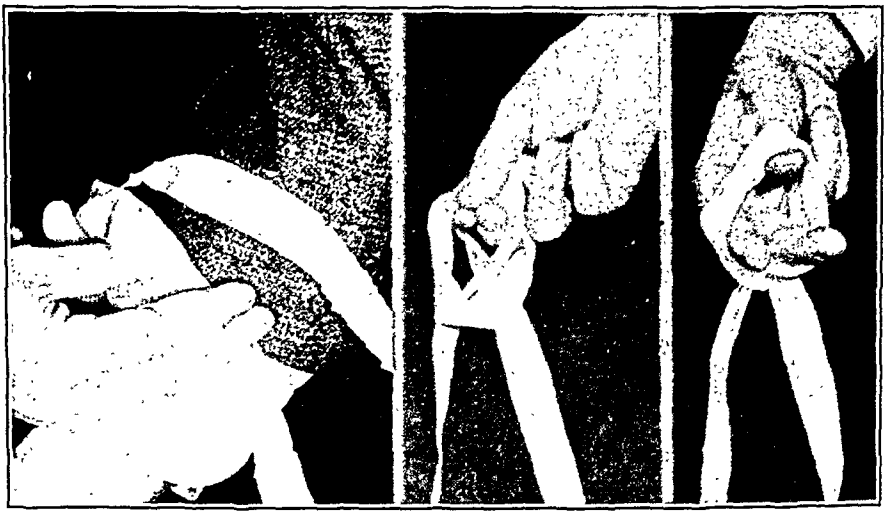


Fig. 3. Fig. 4. Fig. 5.

The two fingers of the right hand now have a clove hitch tied around them. It is a very easy matter to flex the thumb and pass it through this loop (Fig. 5) and reach out with the right hand and take hold of the part around which the clove hitch is to be placed. Then with the left hand, which has thus been released, the knot may be slipped over the presenting part, adjusted as to snugness, and traction applied.

610 West Randolph Street

NEW TYPES OF CERVICAL APPLICATORS FOR TUBAL INSUFFLATION AND UTEROSALPINGOGRAPHY

Emmett D. Colvin, M.D., Atlanta, Ga.

(From the Department of Obstetrics and Gynecology of the Emory University School of Medicine)

TO THE gynecologist and obstetrician, tubal insufflation and uterosalpingography occupy a prominent place in his armamentarium of diagnostic and therapeutic procedures. These two procedures enable him to determine the patency of the oviducts, visualize the uterine cavity, the site of tubal obstruction and serve in the differentiation of uterine from extrauterine masses. Both are indispensable in the diagnosis and treatment of human sterility.

When performing these procedures, in order to avoid false impressions, leakage at the cervix must not occur. To overcome leakage, using ordinary instruments, it is necessary to make counter traction on the cervix by means of a volsellum forceps. This is painful to the patient and traumatizing to the cervix. Another means of avoiding leakage is by pressing the cannula more firmly inward against the cervix during the test. When a short stemmed cannula is used this is objectionable as it

stated that the heads presented and that they both delivered at the same time without aid. She also stated that it was born dead. The monster weighed 3,300 gm.

The mother was a colored woman, gravida iv, para iii; the other three children were normal. Duration of labor was fourteen hours. The perineum was inspected by a physician several hours after delivery of the monster, and he found a first degree laceration from a previous delivery with only a slight tear of the mucous membrane from the birth of the monster.

A ONE-HANDED CLOVE HITCH FOR OBSTETRIC MANEUVERS

LE MON CLARK, M.D., CHICAGO, ILL.

IN THE case of a footling presentation or where, for any reason, it is desirable to put a fillet of gauze around the foot or hand of a fetus during the process of labor or delivery, the knot of choice is the clove hitch. With such a knot the fillet may be adjusted to just the right snugness so that circulation will not be cut off and yet tight enough so that it will not pull off. Such a knot will not slip, and thereafter no amount of traction will cause the loop around the presenting part to become any tighter.

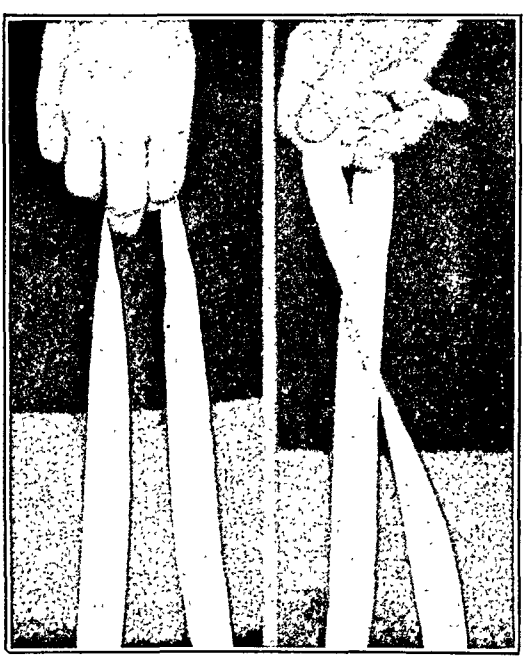


Fig. 1. Fig. 2.

This, of course, is not true of the ordinary slip knot which is so commonly used because it is easy to make and may be made with one hand. Such a knot may slip so that it tightens around the part, causing trouble by impeding the circulation.

There is a method of tying a one-handed clove hitch that is extremely simple. The story of how it was learned is an amusing one. While visiting in Ireland last summer, a group who had had dinner together were staging a round of parlor tricks. When the subject of rope and string tricks came up, a British Army Major contributed the one-handed clove hitch. He, of course, had no appreciation of its value to an obstetrician. But for situations mentioned above, it is most useful.

While the left hand holds the part over which the fillet is to be placed, take a piece of gauze about three feet in length and, holding it around the index and middle

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Endocrinology

Dodds, E. C.: The Sex Glands. Their Anatomy, Physiology, and Biochemistry, Brit. M. J. 2: 163, 1937.

A brief discussion of the sex hormone products available in the commercial market is presented. Two sets of hormone substances are connected with the physiology of the sex glands. First, there are those of the anterior lobe of the pituitary gland which activate the secondary sex glands; and second, those secreted by the sex glands after activation.

The hormones of the anterior lobe of the pituitary to date are not available for clinical trial. Experimental work on animals indicates that such extracts of the gland are capable of producing ovulation and corpora lutea in the female, and descent of testis and spermatogenesis in the male.

In the pregnancy urine of certain species the luteinizing fraction of the gonadotropic substance of the anterior pituitary, prolan B, occurs. The blood serum of the pregnant mare during certain stages of gestation contains a very active ovary-stimulating factor. This is available for clinical trial in a stable and standardized form.

The hormones of the ovary are estrone, estradiol, and progesterone. Estrone and estradiol differ one from the other in relative potency only. Estradiol is the more potent of the two. They are available clinically in the form of benzoates. With the administration of estrone or estradiol followed by corpus luteum hormone (progesterone) the menstrual cycle may be reproduced in ovariectomized females. Relatively high dosage of the hormones is required.

The male sex hormone, testosterone, is briefly discussed.

The substances are best absorbed in the body when administered in oily solutions.

F. L. ADAIR AND S. A. PEARL.

Dawson, J. B.: Endocrinology in Obstetrics and Gynaecology, New Zealand M. J. 36: 9, 1937.

The author presents a concise summary of the present status of the estrogenic hormones and their application in clinical fields. He deals with the use of hormones in habitual abortion, hyperemesis gravidarum, toxemia of late pregnancy, and induction of labor.

Sex hormones are discussed in connection with treatment of amenorrhea, oligomenorrhea, functional uterine bleeding at puberty and at the menopause, dysmenorrhea, the menopause, pruritus vulvae and leucoplakia vulvae, gonococcal vaginitis, especially in children; and other rare conditions.

In the use of endocrine therapy, as in every other department of medicine, every case must have individual study and evaluation of dosage.

F. L. ADAIR AND S. A. PEARL.

is a frequent source of error. Upward pressure on the cervix causes increased obstructing angulation in the uterocervical canal as the result of counter traction on the uterus by the round ligaments. Also, if upward pressure is too strong during uterosalpingography it will cause peculiar x-ray shadows of the uterine cavity.

With these difficulties in mind the author devised and has extensively used the instruments pictured in Fig. 1. They are made of stainless steel. They have clinically proved most satisfactory, having replaced instruments previously used in his office. Insertion into the cervix is practically painless.

The stems are provided for the attachment of either a Luer syringe or rubber tubing. Thus they can be used for air insufflation or for the injection of opaque media into the uterus and tubes during uterosalpingography.

A common stem with three graduating interchangeable tips is provided (Fig. 1). These have proved to be much more satisfactory than the olive tipped cannula.

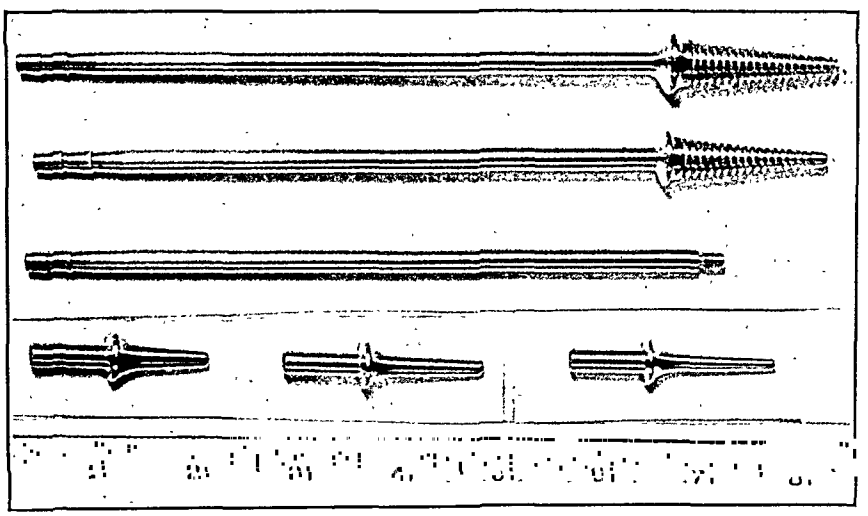


Fig. 1.

Above, two screw tipped stems are seen. These are made in two sizes, large and medium. These two instruments fulfill all requirements. They insure against leakage, cause very little pain during gradual insertion and do not damage the canal. The heads are not detachable from the stems. The screw tip is inserted by gradual rotation in a clockwise direction until slight resistance is felt. Rarely is it necessary to advance the tip to the level of the internal os. With the instrument screwed into the canal, if desired, it is possible to pull the cervix downward during insufflation or injection.

During salpingostomy operations, with the stem screwed into the cervix, the operator can under manometric control inflate the tubes by means of a sterile bulb from the operative field. Thus the actual point of obstruction can be detected after opening the abdomen.

NOTE: These instruments are made by T. L. Keith of Atlanta, Ga.

1259 CLIFTON ROAD, N.E.

Foss, George L.: Temporary Postponement of Menstruation by Oestradiol Benzoate, Brit. M. J. 2: 10, 1937.

There are occasions when temporary postponement of menstruation is greatly desirable and justifiable. The author favors such therapy once or twice only during an individual's lifetime.

He obtained good results by the use of 50,000 I.B.U. of estradiol benzoate (six times as physiologically active as estrone). The standardized preparation used in this work was progynon B oleosum. The injections are best given at close intervals on alternate days, especially towards the expected time of onset, and even after ovulation takes place good results are possible with large doses.

Such a temporary inhibition of the anterior pituitary by estrin does not seem deleterious, according to the author's experience. Injections must be made intramuscularly, especially in obese patients, to avoid leakage from the tissues. The essence of this therapy is to maintain a high superthreshold level of estradiol benzoate until after the time when menstruation is expected.

F. L. ADAIR AND S. A. PEARL.

Westman, A.: The Effect of the Gonadotropic Anterior Pituitary Hormone Antex on the Ovaries of Women, Acta obst. et gynec. Scandinav. 17: 492, 1937.

Westman administered Antex which is a gonadotropic anterior pituitary hormone to women who were to be operated upon. He then removed the ovaries and studied them. In seven women he found an increased follicle growth in the ovaries after the injection of the gonadotropic hormone. Of 7 women who had myomas, 5 showed excessive follicle formation in the ovary after the injections. Hence the effect of gonadotropic hormone on the human ovary is the same as it is on the ape ovary. This effect was produced in normally functioning ovaries. The author is now trying to find out if the same effects can be produced in cases of primary and secondary amenorrhea.

J. P. GREENHILL.

Hamblen, E. C., and Ross, R. A.: Responses of the Human Ovary to Gonadotropic Principles, Endocrinology 21: 726, 1937.

An analysis of observations upon 85 patients after gonadotropic therapy and of detailed reports of the ovarian responses of 7 patients is made. Six of the 7 cases reported in detail were patients in whom presumptive diagnoses of anovulatory failure had been made. The total doses in these patients ranged from 6,000 to 24,250 R.U., the daily doses varying from 400 to 8,000 R.U. The observed ovarian responses, judged either by direct inspection of ovaries, by their microscopic study, or by inferential studies of the endometrium, do not warrant an assumption that ovulation and corpus luteum formation had resulted from such therapy.

J. THORNWELL WITHERSPOON.

Moricard, F., and Saulnier, F.: Follicular Development in the Ovary of Women Stimulated by Injections of Mitosine (Gonadotropic Hormone From the Serum of Pregnant Mares), Bull. Soc. d'obst. et de gynéc. 27: 132, 1938.

In 1937 Moricard and Saulnier published a paper reporting that they had been able to stimulate follicular development in women by means of gonadotropic hormone of serum from pregnant mares. In the present paper the authors give the details of their work on more than 2,000 animals. They observed: (1) In gravid mares there is a hormone in the serum which is capable of stimulating massive follicle development in immature mice. (2) When this substance is injected in doses of 1/1,000 mg., it can cause a tenfold increase in the weight of the uterus of immature mice. (3) The response of the ovary to the action of mare's serum is variable.

The authors give case reports of four women treated with serum from pregnant mares to prove that this serum can produce follicle development.

J. P. GREENHILL.

Boycott, M., and Rowlands, I. W.: The Biological Nature and Quantitative Variation of the Gonadotropic Activity of Pregnant Women's Serum, Brit. M. J. 1: 1097, 1938.

It is shown, in contrast to pregnant mare serum extract, that extracts of human pregnancy serum behave similarly to extracts of urine of pregnancy, in that, (1) they cause only a limited response in the rat ovary, judged by increase in ovarian weight, and (2) they produce no follicular growth in the ovary of the hypophysectomized rat.

The concentration of gonadotropic substance in human serum rises rapidly from the sixth week, is at a maximum from the eighth to the twelfth weeks, and thereafter declines to a low level, which is fairly constant from the twentieth week to the end of pregnancy.

No gonadotropic substance was detected in serum of nonpregnant women.

The significance of the presence of gonadotropic substance in relation to the luteal activity of the placenta is discussed.

F. L. ADAIR AND S. A. PEARL.

Bowes, Kenneth: Treatment of Menstrual Irregularities by a New Sex Hormone Preparation, Brit. M. J. 2: 904, 1937.

The author reports a small series of cases in which the hormone obtained from pregnant mare serum (the follicle-stimulating hormone of the hypophysis) was used successfully in the treatment of menstrual disorders. The product used was "antostab."

Results of the therapy were studied by clinical means and by the strip-cutting curette of uterine biopsy for microscopic changes. While the series is too small for definite conclusions, the results are gratifying and justify mention.

F. L. ADAIR AND S. A. PEARL.

Davidson, Stephen M.: Oestrin and Progestin in Secondary Amenorrhoea, Brit. M. J. 2: 1190, 1936.

The author describes 4 patients in whom the administration of large doses of estrin produced menstruation, following a secondary amenorrhea in 2; one incompletely established menses, and one failure. Owing to the expense, the treatment is applicable only to a few select patients. These experiments further elucidate the action of the ovarian secretions upon the endometrium and the role they play in the menstrual cycle.

The estrin is responsible for the growth and development of the uterus. It is of value clinically in sexually immature and underdeveloped individuals. Progestin has been established as the factor required to produce the glandular changes in the endometrium which must take place before the endometrium can harbor and embed a fertilized ovum. It must, therefore, be a part of the therapeutic regime in amenorrhea and sterility. Only a small dose of progestin is required in clinical use—5 units; whereas, estrin must be given in huge doses, i.e., up to one million I.U. to establish a cycle. Different workers vary in the dosage advised.

F. L. ADAIR AND S. A. PEARL.

Koch, W.: Hormonal Influence of Sex in the Dog, Klin. Wchnschr. 15: 1135, 1936.

The author describes a series of experiments in which he attempted to influence the sex of subsequent litters in a large series of dogs. These animals were fed large quantities of the follicle hormone and the percentage of males in the subsequent litters was compared with the percentage of males in previous litters. These previous litters showed 84.7 males to every 100 females. Following the administration of the hormone the ratio changed to 126.5 males for every 100 females, an increase of over 50 per cent. It would seem, therefore, to be possible to influence or change the sex of subsequent offspring by hormonal administrations.

RALPH A. REIS.

Heiberg, B.: The Excretion of Gonadotropic Hormone in the Urine of Women After Ovarian Autotransplantation, Acta obst. et gynec. Scandinav. 17: 440, 1937.

In agreement with others, B. Heiberg found that when the amount of gonadotropic hormone in the urine is increased beyond fairly low values, it is as a rule a sign of decreased ovarian function. He examined the urine of five women in whom autotransplantation had been performed. He found that for several weeks after operation there was no increase in the excretion of gonadotropic hormone. Then during the next few months there was an increased amount of this hormone corresponding to a diminished function of the implanted tissue because of insufficient adhesions. Then for many months there was a diminution in the amount of the gonadotropic hormone which proved that the transplant was functioning as normal ovarian tissue. Finally in all five patients, increased amounts of the hormone appeared in the urine indicating decreased activity of the transplants. Apparently the climacteric was setting in. The clinical symptoms which these patients exhibited corresponded with the hormone studies.

J. P. GREENHILL.

Kosakae, J., Okamoto, S., and Kosuge, T.: Are the Sexual Hormones Excreted Through the Sweat Glands? Jap. J. Obst. & Gynec. 20: 279, 1937.

It has been demonstrated that the sex hormones and the hormones of the anterior pituitary gland are absorbed through the skin. It has also been shown that there is a connection between absorption through the skin and the presence of sweat glands. The authors attempted to find out whether the sex hormones were eliminated through the sweat glands because they looked upon these glands as avenues of excretion just as the urine is. In order to collect large quantities of sweat they placed their patients in heat chambers. The authors examined the sweat of three women over a period of many weeks but failed to find a trace of the female sex hormones. They likewise analyzed the sweat of five men for anterior pituitary hormones but could not detect any of these hormones.

J. P. GREENHILL.

Venning, Eleanor Hill, and Browne, J. S. L.: The Urinary Excretion of Sodium Pregnandiol Glucuronidate in the Human Menstrual Cycle, Endocrinology 21: 720, 1937.

The quantitative excretion of sodium pregnandiol glucuronidate in the human menstrual cycle in 10 cases is reported. This compound is considered to be an excretion product of progesterone. It is only excreted in the luteal phase of the menstrual cycle and appears in the urine within twenty-four to forty-eight hours after ovulation. The excretion of this compound is continuous for a certain period, varying from three to twelve days in the cases studied; in 6 of the 10 cases the period was ten to twelve days. Bleeding occurs from one to three days following its disappearance from the urine. The total amount of pregnandiol excreted per period varied from 3 to 54 mg. The measurement of this compound in the menstrual cycle offers a means of determining the duration and functional activity of the corpus luteum.

J. THORNWELL WITHERSPOON.

Englehart, E., and Riml, O.: The Metabolic Function of the Corpus Luteum, Arch. f. Gynäk. 164: 36, 1937.

It had been previously reported by the authors that corpus luteum extracts produce changes in metabolism and they had, therefore, concluded that the corpus luteum has a direct effect upon metabolism. Further studies led them to report that the changes in metabolism previously reported were due to some as yet un-

Costa, P., and Cantilo, E.: Inhibition of Friedman Test by Large Doses of Theelin, Compt. rend. Soc. franç. de gynec. 8: 19, 1938.

The authors report a case in which they caused a positive Friedman test to become negative by giving large doses of theelin. The test became again positive as soon as the theelin injections were stopped. Therefore it is proved that the secretion of the gonadotropic hormone of the anterior pituitary can be inhibited by large doses of theelin.

In spite of the huge doses of estrin administered, an abortion did not take place. This the authors attribute to the use of large amounts of corpus luteum after the theelin was given. These authors found that abortion frequently followed the administration of large amounts of theelin when corpus luteum was not subsequently used.

J. P. GREENHILL.

Neuman, Hans Otto: Adrenal Cortex and Sexuality, Arch. f. Gynäk. 160: 481, 1936.

Adrenal cortex deficiency produces a hypofunction of sex function which leads to atrophy of the glands and to amenorrhea. The author describes a patient with Addison's disease in whom he found a menopausal type of atrophy of the uterine mucosa. Hormonal therapy resulted in a restoration of functioning endometrium and a return of normal menstrual flows.

Hyperfunction of the adrenal cortex produces precocious puberty in children, virilismus and interrenalism in the sexually mature woman, but practically no changes in sex characteristics after the menopause. The author describes three cases of hypernephroid blastomas. One of these patients had undergone marked masculinizing changes which disappeared after removal of the tumor. She subsequently became pregnant and had a normal full-term child.

The author also describes three hypernephroid blastomas of the ovaries. He discusses the causes of this typical masculinizing effect of hypernephroid blastomas and concludes that their effect is produced indirectly by way of the hypophysis.

RALPH A. REIS.

Moricard, R.: Trophic Disturbances in the Genitalia Secondary to Hypophysectomy in a Woman, Bull. Soc. d'obst. et de gynéc. 25: 777, 1936.

The author reports the case of a woman who had a hypophysectomy done because of a tumor. There had never been any functional disturbances in the genitalia, but following the operation there resulted an atrophy of the entire genital tract.

J. P. GREENHILL.

Krane, W.: Investigations in the Effects of Hysterectomy on the Endocrine Functions of the Ovary and the Pituitary in the Mature Woman, Arch. f. Gynäk. 164: 101, 1937.

The author describes a new and much shorter method for the quantitative determinations of estrogen content and contrasts it with the previous standard method, i.e., benzol extraction. He then reports his findings in patients in whom hysterectomy was performed during the reproductive years. There is no increase in prolan production which is evidence that ovarian atrophy does not set in after hysterectomy. The production of estrogen continues at its normal level for years following hysterectomy. The latter does not, therefore, induce any castration effect. Studies carried out over a 54 day cycle in a patient who had undergone hysterectomy six years previously showed the normal and usual variations in the estrogen level. The cyclic curves of increased and decreased production of estrogen followed the normal curves and the author concludes that ovulation continues normally after hysterectomy.

RALPH A. REIS.

revealed greater damage than in controls not receiving the sensitizing injections. The effect of the gonadotropic hormone was absent in spayed animals. Progesterone did not prevent the sensitizing effect of estrin, and testosterone propionate seemed to augment the effect.

The author states that the sensitivity of the rat to toxic doses of vasopressin can be greatly enhanced by preliminary treatment with estrogenic hormone. It is recalled that the injection of vasopressin causes eclampsia-like lesions in animals, that the eclamptic patient is said to be hypersensitive to vasopressin and that the period of pregnancy in which eclampsia is peculiar is characterized by a high output of estrogenic hormone. It is suggested that estrin-sensitization may be in some way concerned with the genesis of eclampsia.

CARL P. HUBER.

Gonnet, Bansillon, and Bucher: New Observations on the Use of Estrogenic Substance for Inducing Labor, Bull. Soc. d'obst. et de gynéc. 26: 514, 1937.

The authors report eight instances in which they induced labor by means of estrogenic substance. In one case a single injection resulted in the expulsion of a fetus which had been dead for some time. The other seven inductions were in women with contracted pelves. There was only one failure. To obtain successful results with estrogenic substance it is necessary to purge the patient and then give quinine and pituitary extract. The authors believe there are no dangers associated with this procedure.

J. P. GREENHILL.

Cotte, G., Mileff, A., and Meyer, C.: The Action of Folliculin on the Vaginal Mucosa of Women, Rev. franç. de. gynéc. et d'obst. 32: 683, 1937.

The authors have shown that in women administration of estrogenic substance alone suffices to produce mucification of the vaginal epithelium and the reappearance of glycogen in it. In some of the authors' patients the ovaries were absent, hence the effect on the vaginal mucosa was due entirely to the injected estrin. These results agree with those obtained by Papanicolaou and by Klaften whose work was unfamiliar to the present authors until they had completed their studies. The effects produced on the vaginal epithelium by estrin may be used not only to select proper cases for estrin therapy but also to judge the effectiveness of this kind of treatment.

J. P. GREENHILL.

Wilde, H., and Wolf, B.: The Hormone Treatment of Gonorrheal Vulvovaginitis in Children, Med. Klin. 33: 122, 1937.

The authors treated seven children who had gonorrheal infections with estrogenic hormone. Five children had an infection of the vagina and urethra, one had the infection in the vagina, urethra, and rectum and the seventh had an isolated vaginal gonorrheal infection. All of these children were given 10,000 unit doses of estrogenic hormone in addition to local treatment. The results were not favorable. Furthermore complications were observed. All the children had swelling of the breasts, which subsided after the hormone treatment was stopped. Two children (aged 9 and 11) began to masturbate vigorously. In both children the labia and clitoris were markedly swollen. The authors' experience led them to believe that hormone therapy in young girls results in long-standing disturbances in the glands of internal secretion, because in their cases physical and psychic changes persisted for many weeks. Only the future can tell whether disturbances will manifest themselves during the reproductive years.

J. P. GREENHILL.

Cesa, I.: Influence of Hormonal Action on the Cervical Glands, Compt. rend. de la Soc. franç. de Gynéc. 6: 266, 1936.

In animals there exists a great variation in the condition of the cervix. This region is always badly differentiated in immature animals and among castrated

defined chemical in the lipoid extract and not to the corpus luteum hormone. They report further that the corpus luteum has no effect upon thyroid function but does effect glycogen storage in the liver, by producing an increase.

RALPH A. REIS.

Macht, David I.: Methods of Demonstrating the Activity of Corpus Luteum, Surg. Gynec. Obst. 66: 733, 1938.

A résumé of all kinds of experimental data found in scientific literature regarding the physiologic function of the corpus luteum is presented.

Three lines of investigation by the writer and his collaborators with water-soluble corpus luteum preparations are described.

A study of vaginal smears revealed that injections of corpus luteum extracts distinctly inhibited the estrus cycle of guinea pigs.

Injection of corpus luteum extracts in mice inhibited a tendency to hypertrophy of the uterus induced by injections of estrogenic follicular extracts.

Corpus luteum extracts elicited characteristic responses from uterine muscle of guinea pigs and cats, Fallopian tubes of pigs, and vasa deferentia of white rats.

In the three classes of experiments the same extracts induced parallel and comparable results, thus demonstrating that the activity of corpus luteum preparations may be shown by several convenient methods.

WILLIAM C. HENSKE.

Haffner, J.: The Progestin Content of Mature and Immature Human Placentas, Acta obst. et gynec. Scandinav. 18: 25, 1938.

The author made quantitative determinations of progestin in full-term placentas and found that there was on an average a one-half Clauberg rabbit unit present in each placenta. In placentas obtained from pregnancies in the first three months, he found an average progestin content in each placenta of between one-third and one-half Clauberg rabbit unit. The author, therefore, maintains that progestin is formed in the placenta in the early months and he believes that habitual abortions are due to failure on the part of the placenta to produce progestin.

J. P. GREENHILL.

Jeanneny, G., Hirtz, G., and Merveille, P.: Reflections on the Uterine Hormone Functions, Rev. franç. de gynéc. et d'obst. 32: 149, 1937.

The authors raise the question as to whether or not the uterus possesses an internal secretion. They cite the following as evidence in support of an affirmative answer: The occurrence of metrorrhagia, and even amenorrhea in the presence of fibroids is an evidence of uterine dysfunction. The partial or total conservation of the uterus during gynecologic operations reduces postoperative complications and assures continued function of the ovaries, left behind or grafted. Removal of a uterus results in degeneration of ovaries left in situ.

The authors are convinced of a utero-ovarian functional synergy and they lay down the following rules: Conserve the ovaries and uterus totally or in part as often as possible. In cases of bilateral oophorectomy with conservation of the uterus, always graft an ovary. After hysterectomy with conservation of the ovaries, make a uterine graft. After removal of the uterus and adnexa make a graft of both uterus and ovary. The authors have prepared a uterine extract which they have administered by mouth as well as subcutaneously for dysmenorrhea with good results.

J. P. GREENHILL.

Byrom, F. B.: The Effect of Oestrogenic and Other Sex Hormones on the Response of the Rat to Vasopressin, Lancet 1: 129, 1938.

A group of immature unspayed rats was injected with gonadotropic and a second group with estrogenic hormone following which 50 international units of vasopressin per 100 gm. body weight were injected. Examination of the kidneys in these animals

Loeser, A. A.: Resorption and Action of Follicular Hormone Rubbed Into the Skin, J. Obst. & Gynaec. Brit. Emp. 44: 710, 1937.

His experiments showed that the skin of monkeys (baboons) is penetrable by follicular hormone. Estrus can be produced in castrated monkeys by rubbing the hormone into the skin. In women from whom the ovaries have been removed or in women suffering from ovarian insufficiency, clinical symptoms can be produced by rubbing the hormone into the skin; this indicates that the skin absorbs and is penetrated by the follicular hormone. The skin of women with normally functioning ovaries is penetrable by the follicular hormone to an individually varying degree. There appears to be a connection between ovarian insufficiency and changes in the skin (atrophy). Administration of follicular hormone is of value in skin affections.

J. P. GREENHILL.

Ito, Hajazu and Kon: Percutaneous Action of the Sex Hormones, Zentralbl. f. Gynäk. 61: 1094, 1937.

These writers found that folliculin is absorbed through the skin by female monkeys and rats, so that in them estrus, uterine hypertrophy, and mammary development can be produced. The effect depends somewhat on the vehicle used for the hormone. The most marked effect is obtained from a solution containing 60 per cent of alcohol, while water, skin cream, lanolin and vaseline cause a decrease in strength. The percutaneous method of administration is preferable to the oral when a prolonged effect is desired. The male sex hormones can be equally well administered through the skin.

J. P. GREENHILL.

Migliavacca, A.: Contribution to the Local Therapy of Pruritus Vulvae, Atti. Soc. ital. di ostet. e ginec. 34: 178, 1938.

The author experimented with the action of follicular hormone applied directly to the external genitalia as a salve (lanolin and vaseline used as the vehicle).

The results were somewhat favorable. The accurate selection of cases appeared indispensable for a successful therapeutic result. Pruritus vulvae associated with ovarian dysfunction and with atrophic changes accompanying the menopause is the type of pruritus lending itself most favorably to this form of local treatment.

The author claims as advantages of local treatment that the therapeutic action is more prompt and direct, and requires a smaller quantity of the hormone, hence is more economical.

A. A. MARCHETTI.

Wetterwald, M.: The Hormonal Treatment of Pruritus Vulvae in the Menopause, Rev. franç. de gynéc. et d'obst. 32: 572, 1937.

Wetterwald is convinced that large doses of estrogenic substance will surely and rapidly cure pruritus vulvae during the menopause. He gives an injection of 10,000 international benzoate units (50,000 ordinary international units) every second day. It is important to continue these injections for a while after the pruritus has ceased. In a few cases serious uterine bleeding has been reported but the author has never encountered such a case. This bleeding is to be expected because large amounts of estrogenic substance can produce hyperplasia of the endometrium.

J. P. GREENHILL.

animals. It attains its full development only under the influence of estrogenic substance hence only at estrus. It is at this time that the special characteristics of the cervical glands are most marked. The action of the corpus luteum hormone on the glands consists of stimulation of their secretion. These facts explain the development of the cervix and its glands in women and also the variation found in the cervix at different parts of the menstrual cycle.

Small doses of estrogenic substance stimulate the cervix. Since large doses produce intense changes in the epithelium of the cervix of animals, the author cautions against the prolonged administration of large doses of these substances alone. Corpus luteum hormone produces resolution of these changes hence the danger consists in giving estrogenic substance alone. It is probable that estrogenic substance and the corpus luteum hormones are not the only hormones produced by the ovary, nevertheless, they are antagonistic substances.

J. P. GREENHILL.

Zuckerman, S.: Effects of Prolonged Oestrin-Stimulation on the Cervix Uteri, Lancet 1: 435, 1937.

Carcinogenic power has been ascribed to estrogenic substances, largely because of results occurring in "cancer strains" of mice. Such effects have not been induced in the reproductive organs of women and monkeys by excessive or prolonged dosage with estrogenic substance.

Prolonged and massive dosage of this material results in the development of cystic endometrial hyperplasia. By withdrawing the estrogenic stimulus the changes are reversed.

A review of the report of Overholzer and Allen is given. The author was unable to show any cancerous or precancerous lesions of the cervix in monkeys receiving much larger amounts of estrogenic substances. A metaplasia was noted at the junction of the squamous and columnar epithelium. This metaplasia is orderly, and the basement membranes remain intact.

It is concluded that there is little need in clinical practice for prescribing the hormone over a prolonged period; and the effect of estrin can be reversed by its withdrawal. It is suggested that the best way to administer estrogenic hormone clinically is in courses of two to four weeks with intervals for the "estrin-withdrawal."

H. CLOSE HESSELTINE.

Ziskin, Daniel E.: Effect of Hormonal Treatment on Gums and Oral Mucosa of Women, J. Dent. Research 16: 367, 1937.

The hormones progynon B and follutein injected respectively into women in the treatment of amenorrhea and prolonged menstruation bleeding, affect the gingivae and oral mucosa. Progynon B causes hyperkeratinization and hyperplasia of the oral epithelium. The gums of women receiving progynon are uniformly in a healthier state than those receiving follutein. The gums of women receiving the latter hormone show evidence of inflammation and degeneration both grossly and microscopically, probably as result of a direct effect of follutein.

These findings made on six women resemble closely previously reported observations of the author made on female rhesus monkeys.

HUGO EHRENFEST.

Moricard, R., and Cauchoix, J.: Macroscopic Fibroids Obtained Experimentally in the Rabbit by the Continuous and Prolonged Action of Dihydrofolliculin Benzoate, Bull. de la Soc. d'obst. et de gynéc. 27: 272, 1938.

As indicated by the title the authors were able to produce macroscopic fibroids in female rabbits by continuous injections of the benzoate of folliculin. The doses given were small but the injections were administered over a period of four and one-half to seven months.

J. P. GREENHILL.

Books Received

THE TECHNIQUE OF CONTRACEPTION. An Outline. By Eric M. Matsner, M.D. Foreword by Frederick C. Holden, M.D. Fourth edition, illustrated, 50 pages. The Williams & Wilkins Company, Baltimore, 1938.

DER ZYKLUS DER FRAU. Reform des Ehelebens. Von Dr. Jules Samuels, Chirurg-Frauenarzt. Mit 43 Abbildungen im Texte, 175 Seiten. Verlag G. Naeff, Haag, Holland, 1938.

THE VITAMINS AND THEIR CLINICAL APPLICATIONS. A Brief Manual. By Professor Dr. W. Stepp, director of I. med. Klinik, University of Munich, Dozent Dr. Kuehnau, in Wiesbaden, and Dr. H. Schroeder, Associate, I. med. Klinik, Munich. Translated by Dr. Herman A. H. Bouman, Minneapolis, Minn. The Vitamin Products Company, Milwaukee, Wis., 1938.

CANCER, With Special Reference to Cancer of the Breast. By R. J. Behan, M.D., F.A.C.S., Cofounder and formerly director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation. Illustrated, 844 pages. C. V. Mosby Company, St. Louis, 1938.

THE ROCKEFELLER FOUNDATION. Annual Report, 1937. New York, 1938.

THE PRINCIPLES AND PRACTICE OF OBSTETRICS. By Joseph B. DeLee, professor of obstetrics and gynecology, emeritus, University of Chicago, etc. Seventh edition, entirely reset. 1211 pages with 1277 illustrations on 985 figures, 271 of them in color. W. B. Saunders Company, Philadelphia, 1938.

STOECKEL'S HANDBUCH DER GYNAEKOLOGIE. Dritte, voellig neubearbeitete und erweiterte Auflage. Zehnter Band. Gynaekologischer Beitrag zur Urologie von Dr. W. Stoeckel, Universitaet Berlin; I. Teil, 738 Seiten mit 432 Abbildungen; II. Teil, 438 Seiten mit 261 Abbildungen; III. Teil, 1008 Seiten mit 468 Abbildungen. Verlag von J. F. Bergmann, Muenchen, 1938.

THE NEW-BORN INFANT. A Manual of Obstetrical Pediatrics. By Emerson L. Stone, M.D., associate clinical professor of obstetrics and gynecology, School of Medicine, Yale University, etc. Second edition, thoroughly revised, 291 pages, not illustrated. Lea & Febiger, Philadelphia, 1938.

TEXTBOOK OF ANATOMY AND PHYSIOLOGY. By Diana Clifford Kimber, Carolyn E. Gray, A.M., R.N., and Caroline E. Stackpole, A.M., associate in biology, Teachers College, Columbia University. Tenth edition, revised and rewritten. 276 illustrations, 643 pages. The Macmillan Company, New York, 1938.

SEASON OF BIRTH. Its Relation to Human Abilities. By Ellsworth Huntington, Yale University. 473 pages with 104 figures. John Wiley & Sons, Inc., New York, 1938.

LIFE AND LETTERS OF FIELDING H. GARRISON. By Solomon R. Kagan, M.D. With an Introduction by Professor James J. Walsh. 287 pages, The Medico-Historical Press, Boston, 1938.

Correspondence

To the Editor:

I have read with great interest the editorial entitled "The Dosage of the Estrogens," which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 36: September, 1938. The confusion that arises, as you point out, from the various trade names of these estrogenic compounds has become extensive, and the addition of another international unit for standardization of these preparations has not helped this situation. In order to assist, if possible, in the clarification of this situation, may I refer to the following points in the above-mentioned editorial?

In the first and third paragraphs, theelol is indicated to be synonymous with estradiol, whereas in fact, it actually is a different compound. Theelol is estriol and constitutes a third type of estrogenic preparation with characteristic physiological properties differing from estrone or estradiol.

In the definition of the international unit in the third paragraph there is undoubtedly a misprint, that is, "0.1 gamma (1/10,000 of a gram)" should read 0.1 gamma (1/10,000,000 of a gram) or (1/10,000 of a milligram). A more important consideration than the definition of the international unit is the fact *that two international units of estrogenic materials have been established,* one for estrone, the other for estradiol. Both units have the same mass (0.1 gamma) but refer to different chemical entities. The quantitatively different physiological potency of these compounds is not apparent when expressed in international units. For example, 1000 I.U. of estrone (theelin) are not equivalent to 1,000 I.U. of estradiol (progynon).

The separation of the various commercial products you have mentioned into the proper class of estrogens may be of interest.

Amniotin and theelin: estrone or ketohydroxyestrin

Theelol and emmenin: estriol

Progynon B and DH, and menformon: estradiol.

Sistomensin, while carrying some estrogenic activity, from a clinical point of view can hardly be regarded as a satisfactory source of this material (Wiesbader and Kurzrok, Endocrinology 23: 32, 1938).

I am forwarding this information to you not as a criticism of your editorial but as an addition to it, in the hope that it will aid in the resolution of the confusion you have pointed out.

Jack M. Curtis,
Associated Pharmacologist, United States
Department of Agriculture.

Washington, D. C.
Nov. 12, 1938

NOTE: It would be desirable if international authorities were able to enforce the use of the simple chemical names of estrone, estradiol, and estriol and urge that these be substituted for the generally employed trade names. Clarification undoubtedly would follow this procedure and further confusion be avoided.

Editor.

American Congress on Obstetrics and Gynecology

Cleveland, Ohio, September 11 to 15, 1939
Preliminary Program

Five-day sessions are planned, mornings from 9 A.M. to 11 A.M., with special programs devoted to professional groups; noon, from 11:45 A.M. to 1:15 P.M., round table discussions; afternoons, 2:30 P.M. to 4:30 P.M., joint sessions of general interest to all members attending the Congress; evenings, Monday through Thursday, 8:30 P.M., speakers of national prominence—open to all members and the public.

In the Medical Section, the following topics will be considered—further details will appear in later issues as these become available:

Monday, September 11, 1939

The Thyroid and Pregnancy; Heart Disease and Pregnancy; Diabetes and Pregnancy; Tuberculosis and Pregnancy; Nutritional Factors and Pregnancy; The Surgical Abdomen Complicated by Pregnancy; The Treatment of Abortions.

Tuesday, September 12, 1939

The New Conception of Ovarian Neoplasms; Carcinoma of the Uterus; Endometriosis; Ectopic Pregnancy; Sterility in the Female.

Wednesday, September 13, 1939

Reduction of the Operative Incidence in Obstetrics; Labor Complicated by the Contracted Pelvis; Dystocia Due to Soft Parts; Pathology and Treatment of the Third Stage of Labor.

Thursday, September 14, 1939

Present-Day Fundamental Knowledge of Hormones and Endocrine Glands; Problems of Adolescence; Problems of Menopause; Diseases of the Mammary Gland.

Friday, September 15, 1939

Sulfanilamide in Obstetrics and Gynecology; Pyelitis; Chronic Pelvic Infections; Immediate and Remote Complications Following Labor.

Round Tables

Running concurrently each day 11:45 A.M. to 1:15 P.M.

The Toxemias of Pregnancy; Genital Infections; Obstetric and Gynecologic Hemorrhages; the Fetus and the Newborn; Forceps, Occipito-Posterior, and Breech Presentation; Anesthesia, Analgesia and Amnesia in Labor.

Joint Afternoon Sessions

Monday, September 11, 1939, Neonatal Care.
Tuesday, September 12, 1939, Plans for Prevention and Control of Uterine Cancer.
Wednesday, September 13, 1939, Extension Education on Maternal and Neonatal Care.
Thursday, September 14, 1939, Economic Aspects of Maternal Care.
Friday, September 15, 1939, Correlation of and Attempt to Digest All Proceedings.

Joint Evening Sessions

Monday, September 11, 1939, Legal Aspects of Maternity.
Tuesday, September 12, 1939, Humanitarian Aspects.
Wednesday, September 13, 1939, Sociologic Aspects.
Thursday, September 14, 1939, Ethical Aspects.

Membership

Membership fee is $5, which includes a year's membership in The American Committee on Maternal Welfare and registration in The American Congress on Obstetrics and Gynecology, Cleveland, Ohio, September 11 to 15, 1939. Application for membership in The American Congress on Obstetrics and Gynecology may be made to Headquarters Office: The Annex, 650 Rush Street, Chicago.

Items

American Board of Obstetrics and Gynecology

The general oral, clinical and pathological examinations for all candidates, Part II Examinations (Groups A and B), will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for reexamination must request such reexamination by writing the Secretary's Office before the following date: Part II, April 1, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their first examination.

Application for admission to Group A, May, 1939, examinations must be on file in the Secretary's Office by March 15, 1939.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

The Central Association of Obstetricians and Gynecologists

The Tenth Annual Meeting of this association was held at the Hotel Radisson in Minneapolis, October 6 to 8, 1938. The following officers were elected for the coming year:

President, Ralph A. Reis, Chicago
President-Elect, Jennings C. Litzenberg, Minneapolis
Vice-President, Thomas B. Sellers, New Orleans University Hospital
Secretary-Treasurer, William F. Mengert, Iowa City
Assistant Secretary, Harry J. Davis, Topeka

Dr. William T. Black, a member of the Advisory Editorial Board of the JOURNAL, died at Memphis, Tenn., on December 8, 1938. An extended obituary will be published in a forthcoming issue.

Errata

In the article by Caldwell, Moloy, and D'Esopo "Studies on Pelvic Arrests" in the December issue, page 935, line 27 the word "inefficient" should read "in efficient."

In the legend for Fig. 4, page 937, the description of numbers *3, 4, 5* should read "*3,* medium in the anterior pelvis (in front); *4,* medium in the posterior pelvis (behind); *5,* Low-medium in the posterior pelvis (behind)."

On page 938, line 5, the reference to the numbers in Fig. 4 should read "(Fig. *4A, 5, 4*)."

On page 944, the table should be "Table VIII" instead of Table III.



WILLIAM T. BLACK
1875—1938

Original Communications

THE OCCURRENCE AND SIGNIFICANCE OF NUCLEATED ERYTHROCYTES IN THE FETAL VESSELS OF THE PLACENTA

CARL T. JAVERT, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College, and the New York Hospital)

AN INCREASED number of nucleated erythrocytes in the circulating blood of newborn infants has a definite significance. Starling states that nucleated red cells practically do not occur in the newborn, while Vaughn found 5 per 100 white cells in the first day of life. Parsons states that premature infants have increased numbers in direct proportion to the degree of prematurity. The writer has observed 1,023 normoblasts and 301 erythroblasts per 100 white cells in the hydrops form of erythroblastosis fetalis. Therefore the numerical determination of these cells has diagnostic value.

THE PRESENT STUDY

The venous blood of a series of 400 unselected newborn infants, including 12 twins, and 26 negro infants, was studied; and forms the basis for this report. These infants ranged from 1,080 gm. to 5,350 gm. in weight, and were born in the Woman's Clinic of the New York Hospital between January and April, 1937.

Blood was aspirated from the umbilical vein or one of its branches on the placenta and smears were made and stained by the Wright technique. Normoblasts and erythroblasts were counted, and their number expressed in terms of 100 leucocytes. No white cell counts were made, since we were interested in testing the efficacy of as simple a procedure as possible. It is to be remembered that nucleated red cells are resistant to acetic acid and would be included in the white cell count.

The average number obtained for normoblasts was 8.7, and for erythroblasts 1.1; making a total average number for nucleated erythrocytes of 9.8, or approximately 10 per 100 white cells.

The original purpose of this study was to obtain an average figure for normoblasts and erythroblasts in cord blood of normal infants in order to facilitate the hematologic diagnosis of erythroblastosis fetalis. The prediction of prematurity in infants with an increased number of these cells was anticipated.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

American Journal of Obstetrics and Gynecology

VOL. 37 FEBRUARY, 1939 NO. 2

IN MEMORIAM

WILLIAM T. BLACK
1875-1938

WILLIAM T. BLACK, a member of the Advisory Editorial Board of the JOURNAL, was born January 12, 1875, at Stanton, Tennessee, and died December 10, 1938, at Memphis. While in the midst of an operation, he was seized with a heart attack and died within the hour. A wide circle of personal and professional friends were shocked and saddened by his sudden passing and he will long be remembered by his associates and many friends.

For a number of years he had been connected with the University of Tennessee. He received his medical education at the Memphis Hospital Medical College, which later was absorbed by the University Medical School. Later he became a valued member of the faculty and for the past four years had held the chair of Gynecology. He served faithfully and fruitfully the university of the state in which he was born and educated.

He was well known in his profession far beyond the borders of his own State, and his articles on medical subjects were published in many periodicals and recognized as important contributions in the field of gynecology.

He was a member of many national associations: The American College of Surgeons; The American Association of Obstetricians and Gynecologists; The Southern Surgical Association; The American Board of Obstetrics and Gynecology; and The Central Association of Obstetricians and Gynecologists, of which he had been vice-president. In many of these he held offices and chairmanships and these duties he always performed exceedingly well.

Dr. Black was ex-president and visiting Gynecologist at the Baptist Hospital, Consulting Gynecologist to St. Joseph Hospital, Professor of Gynecology of University of Tennessee, Visiting Gynecologist to John Gaston Hospital, and Visiting Gynecologist to the Shelby County Almshouse.

His charm of personality, his sterling qualities of character and his deep and abiding interest in humanity and his profession endeared him to all. He will be grievously missed by all who were associated with him.

W. T. PRIDE, M.D.

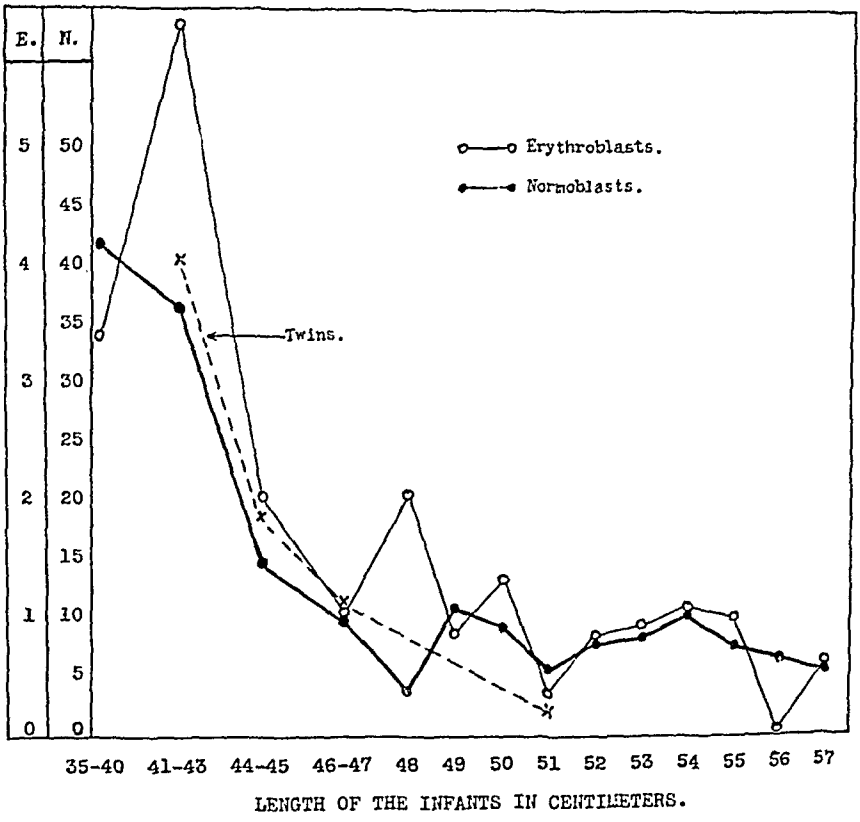


Fig. 2.—The number of erythroblasts (*E*) and normoblasts (*N*) per 100 leucocytes in relation to length.

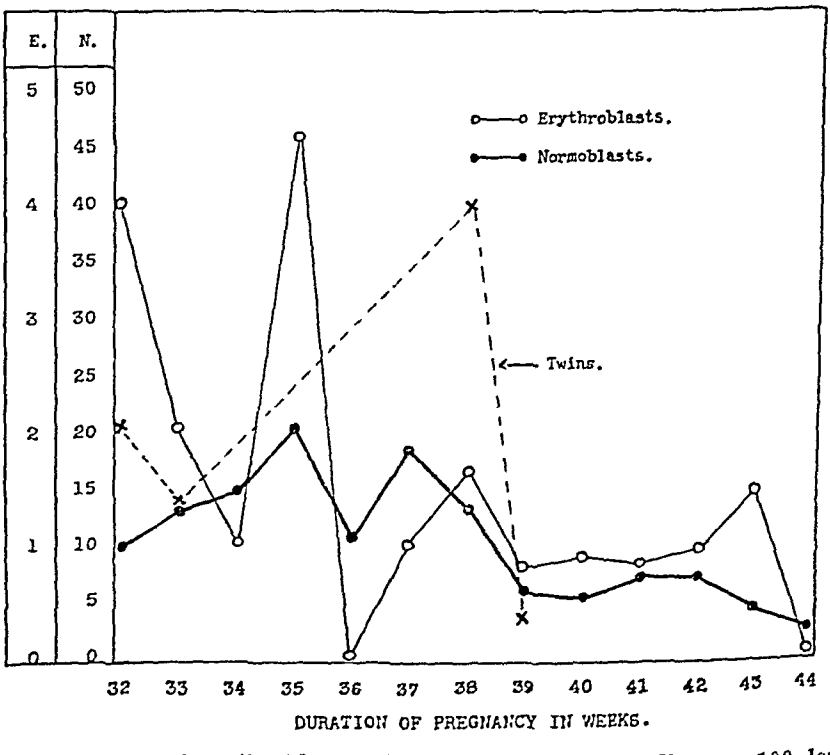


Fig. 3.—The number of erythroblasts (*E*) and normablasts (*N*) per 100 leucocytes in relation to the duration of pregnancy.

STATISTICS

The records of the 400 infants were reviewed after dividing the cases as follows:

Group I, consisting of 275 infants having less than 10 nucleated erythrocytes, serves as the control group. These infants were mature.

Group II, consisting of 125 infants having 10 or more nucleated erythrocytes in whom a greater incidence of prematurity and immaturity was found.

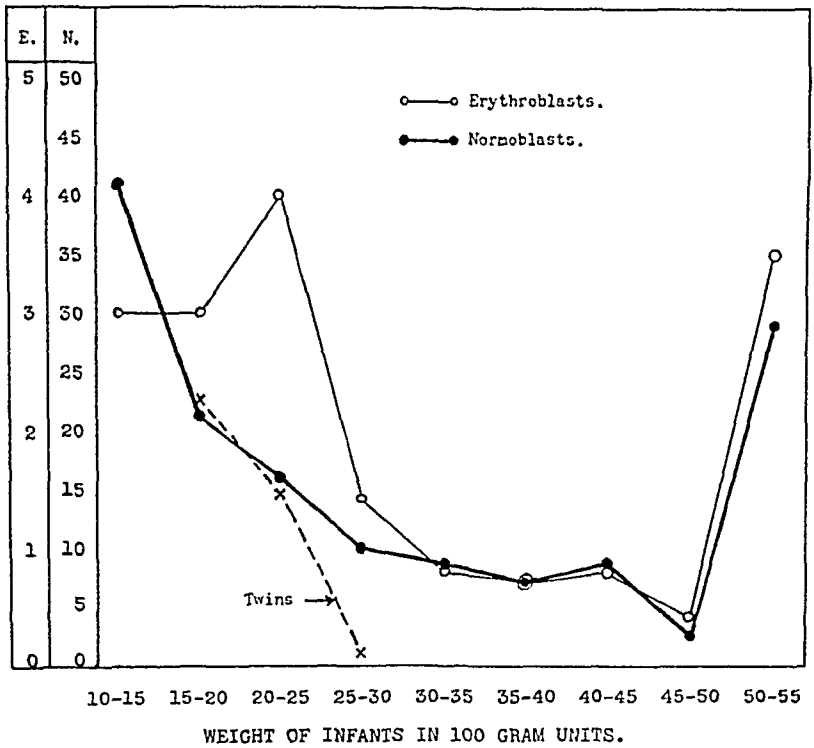


Fig. 1.—The number of erythroblasts (*E*) and normoblasts (*N*) per 100 leucocytes in relation to weight.

Sex.—There was no appreciable difference in either group.

Birth Weight.—The average weight for Group I was 3,429 gm. (7.5 pounds); while in Group II, it was 3,226 gm. (7.0 pounds); or 200 gm. less. Fig. 1 shows the average number of normoblasts and erythroblasts in relation to weight for single and twin infants. The total number of nucleated erythrocytes is less than 10 in the majority of infants weighing over 3,000 gm., and about 20 per cent had no nucleated red cells. The premature infants have an increased number.

Length.—The average crown-heel length in centimeters for Group I was 50.9, and 49.8 for Group II. Fig. 2 shows the average number of normoblasts and erythroblasts in relation to length for single and twin infants. The total number of these cells averages below 10 for infants 48 centimeters in length and over. Infants who are premature as judged by their length, have an increased number of nucleated erythrocytes.

Duration of Gestation.—The expected date of confinement as calculated after the method of Naegele was 39.9 weeks for Group I, and 39.1 weeks for Group II. Fig. 3 shows the number of normoblasts and erythroblasts in relation to the duration of pregnancy for single and twin infants. After the thirty-ninth week of gestation, the average number of nucleated erythrocytes is less than 10. The curves are not as regular as those obtained for weight and length, since the expected date is so often

Twin Pregnancy.—There were 12 twin infants, and their data are presented in Table I. Their normoblastic curves have been shown in Figs. 1, 2, and 3. The curves coincide fairly well with those for single infants with regard to length and duration of pregnancy; but indicate that a twin may be mature at 2,500 gm., instead of 3,000 gm. as for the single infant. Since only 12 twins were studied, this deserves further consideration.

Twins A, B, and C, were considered mature with no fetal mortality, while Twins D, E, and F, were premature and had a mortality rate of 50 per cent. This illustrates a prognostic value for the diagnosis of prematurity and maturity by blood smear.

TABLE I. THE CONSIDERATION OF 12 TWIN INFANTS

	NORMOBLASTS	ERYTHROBLASTS	WEIGHT (GM.)	LENGTH (CM.)	DURATION (WK.)	TYPE	RESULT
				Group I			
Twins A	0	0	2,940	49	39	Double ovum	Well
	2	0	2,810	51	39		Well
Twins B	7	2	2,090	45	39	Double ovum	Well
	2	0	2,220	45	39		Well
Twins C	8	1	2,280	46	39	Double ovum	Well
	2	0	3,010	51	39	Double placenta	Well
Average	3.5	0.5	2,558	47.8	39		
				Group II			
Twins D	24	2	1,840	45	31	Double ovum	Well
	16	2	2,200	45	31		Well
Twins E	40	12	2,120	43	38	Single ovum	Dead
	40	12	1,820	44	38		Dead
Twins F	16	0	1,820	46	35	Double ovum	Well
	10	0	1,890	46	35		Dead
Average	24.3	4.6	1,948	44.8	34.5		

Negro Infants.—The 26 cases had an average weight of 3,225 gm., or 200 gm. less than the clinic average for white infants. Of these, 2 or 7.7 per cent were premature, while the clinic incidence of prematurity is about 3.5 per cent.

On blood smear examination, 12 or 46.0 per cent of the negro infants were considered premature; while 113 or 28.0 per cent of the white infants were premature on this same basis (Group II). This suggests that the higher infantile morbidity and mortality rates in the negro may be due to prematurity.

Mortality Rates.—There were 12 deaths in the 400 infants, 11 white or 2.9 per cent; and 1 negro or 3.8 per cent. This is an uncorrected figure, representing all of the stillbirths and neonatal deaths up to the fourteenth day of life due to any cause. The data are shown in Table II.

Group I consists of mature infants, according to weight, length, and duration of pregnancy, and the number of nucleated red cells, with a ratio of normoblasts to erythroblasts of 10:1. The infants in Group II are premature by these standards, and have a normoblastic-erythroblastic ratio of 6:1, if the case of erythroblastosis is omitted. Autopsy evidence confirms further that prematurity and maturity can be predicted from the blood smear.

Rate of Disappearance of Nucleated Erythrocytes.—There were 7 infants with from 14 to 190 nucleated red cells. All were normal except one, which had hemorrhagic disease of the newborn. The average weight of these infants was 3,494 gm., length 50.1 cm., and duration of gestation of 39.1 weeks. The results of daily

erroneous. The decline at thirty-six weeks suggests that the calculation was one month off, and that these infants were actually at term. The increased number of nucleated red cells in infants under thirty-nine weeks' gestation is significant.

Distribution of Cases.—The percentage of infants in Groups I and II in relation to weight, length, and duration of pregnancy is shown in Fig. 4. About 75 per cent of the infants in Group I were definitely mature, with an average weight of 3,429 gm., length of 50.9 cm., and duration of pregnancy of 39.9 weeks for this group. This leaves about 25 per cent of the infants, in this group considered mature by these standards, in the premature or immature group according to the blood smear examination. This graph also indicates that the nearer the period of conception,

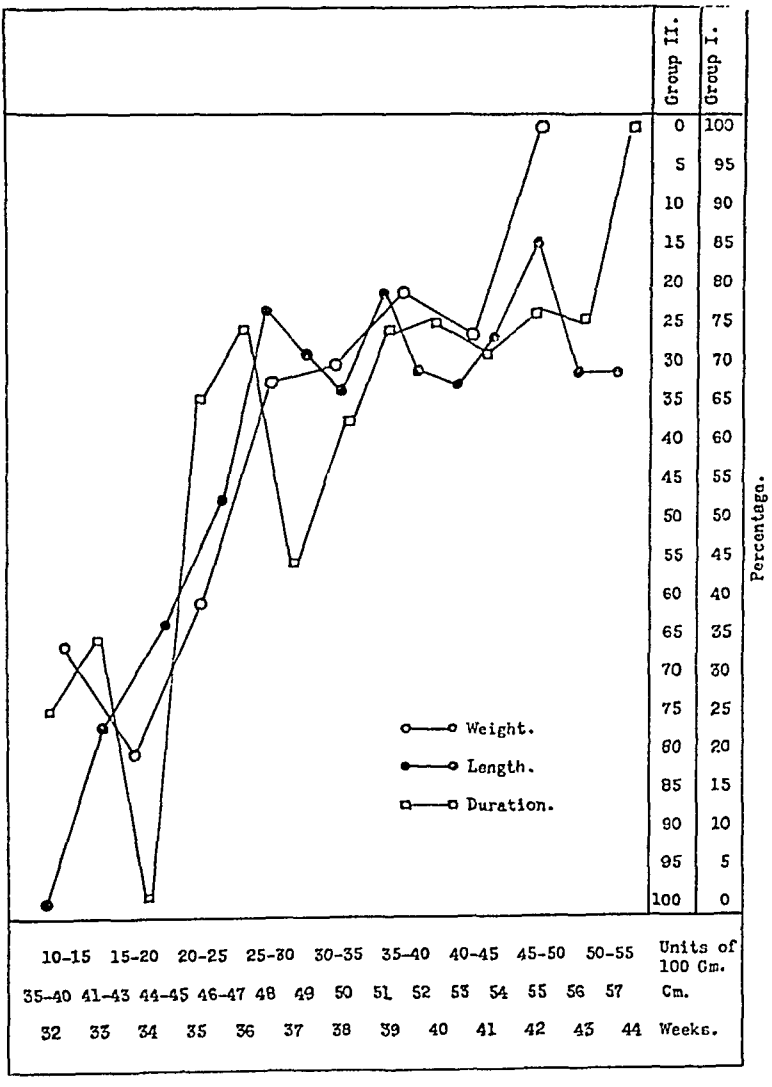


Fig. 4.—The percentage of infants in Groups I and II in relation to weight, length, and duration of pregnancy.

the higher the percentage of infants in Group II. One may conclude that the average number for nucleated erythrocytes is a helpful factor in the determination of prematurity, immaturity, and maturity. However, each case may have its individual variation from the average figure, depending on the individual degree of prematurity or maturity.

Prematurity.—Of 24 infants considered premature by the clinic standards, that is, weighing between 1,500 and 2,500 gm., and between 35 and 45 cm. in length, 8 or 33.3 per cent were in Group I, and 16 or 66.6 per cent were in Group II. This shows an increase of 100 per cent for the second group. Therefore, one-third of the infants considered premature may be mature on blood smear examination.

TABLE IV. A CONSIDERATION OF 8 INFANTS WITH CONGENITAL ANOMALIES

ANOMALY	NORMOBLASTS	ERYTHROBLASTS	WEIGHT (GM.)	LENGTH (CM.)	DURATION (WK.)
Cleft palate, harelip	32	10	2,600	48	42
Anencephalic monster	40	4	1,080	40	37
Pilonidal sinus	16	2	3,190	51	40
Hypospadias, testes undescended	2	0	2,970	49	41
Umbilical hernia	20	6	3,150	50	39
Equino varus	26	2	2,660	48	40
Equino varus	28	2	3,500	54	40
Mongolian idiot	60	10	2,650	45	38
Average	28	4.5	2,725	48	39.6

Ratio of Normoblasts to Erythroblasts.—From the data in Table V, Group I has a ratio of 14:1, while Group II, which has been shown to be more premature, has a ratio of 6.6:1. Infants in Group II who are premature by weight, have a ratio of 6.5:1. The infants who were found to be premature at autopsy have a ratio of 6:1. These average ratios may be of value in addition to the actual increase in nucleated red cells.

TABLE V. THE RATIO OF NORMOBLASTS TO ERYTHROBLASTS

		NORMOBLASTS	ERYTHROBLASTS	RATIO
Group I (275 cases)		2.8	0.2	14 : 1
Group II (125 cases)		12.6	1.9	6.6 : 1
Prematurity by weight	Group I	4.3	0.4	10.8 : 1
	Group II	23.4	3.6	6.5 : 1
Twin pregnancy	Group I	3.5	0.5	7 : 1
	Group II	24.3	4.6	5.3 : 1
Excessive-sized infant	Group I	3.4	0.11	31 : 1
	Group II	21.5	3.0	7 : 1
Infantile deaths	Group I	5.2	0.5	10 : 1
	Group II	37.1	6.2	6 : 1
Erythroblastosis fetalis (3 cases) (1 case in this series)		393.0	109.0	3.3 : 1

Hemorrhagic Disease of the Newborn.—There were 5 cases in this series, giving an incidence of 1.25 per cent. These cases averaged 26.6 normoblasts and 4.6 erythroblasts, with a ratio of 6:1. This is interpreted as evidence of prematurity. The writer has reported an average number of 13 nucleated red cells in smears made on the first day of life from blood obtained by cutaneous puncture from infants with hemorrhagic disease.

Erythroblastosis Fetalis.—One case occurred in this series, giving an incidence of 1 in 400 cases. The cord smear showed 78 normoblasts and 32 erythroblasts, with a ratio of 2.5:1. This infant was delivered in the thirty-third week of gestation by cesarean section, because of premature separation of the placenta. The infant weighed 3,070 gm., was hydropic and dead-born. A diagnosis of erythroblastosis was made from the blood smear, which was substantiated by autopsy.

MATERNAL STATISTICS

The 400 maternal records were studied to determine whether other factors were also to be considered as causes of the increased number of nucleated erythrocytes in Group II. The maternal age, Wassermann reaction, parity, ante-partum weight gain, ante-partum complications, duration of labor, type of delivery, anesthesia, quinine administered

TABLE II. AN ANALYSIS OF THE CAUSES OF DEATH IN 12 CASES

CAUSE OF DEATH	NORMOBLASTS	ERYTHROBLASTS	WEIGHT (GM.)	LENGTH (CM.)	DURATION (WK.)
Group I					
Pre-eclampsia in mother, subarachnoid hemorrhage	0	2	2,620	53	39
Intracranial hemorrhage	6	0	3,130	50	41
Craniotomy, death in labor	9	0	3,470	50	41
Macerated fetus, cause?	6	0	3,670	56	42
Average	5.2	0.5	3,222	52	40.8
	Ratio 10:1				
Group II					
Erythroblastosis fetalis	78	32	3,070	51	33
Harelip, cleft palate, intracranial hemorrhage	32	10	2,600	48	42
Anencephaly, prematurity	40	4	1,080	40	37
Prematurity, bronchopneumonia (twin)	10	0	1,890	46	35
Prematurity	78	6	1,250	38	38
Prematurity, subarachnoid hemorrhage	20	0	2,220	44	38
Prematurity, twin	40	12	2,120	43	38
Prematurity, twin, subarachnoid hemorrhage	40	12	1,820	44	38
Average	42.2	9.5	2,006	44	37.3
Average if erythroblastosis is omitted	37.1	6.2			
	Ratio 6:1				

smears on these infants are shown in Table III. Within a period of 4 days, the nucleated forms had virtually disappeared, without specific treatment, except in the case with hemorrhagic disease which received 40 c.c. of whole blood intramuscularly and recovered.

TABLE III. THE RATE OF DISAPPEARANCE OF NUCLEATED ERYTHROCYTES IN 7 INFANTS

	NORMOBLASTS	ERYTHROBLASTS
Cord blood	69	11
Cutaneous puncture:		
First day	38	2
Second day	24	2
Third day	9	0
Fourth day	1	0

Congenital Anomalies.—These cases are tabulated in Table IV. Only 1 case is in Group I, while 7 are in Group II. This indicates that prematurity rather than the anomaly is the cause of the increased number of nucleated red cells.

Excessive Sized Infants.—Infants weighing over 4,000 gm. were classified as excessive sized infants. There were 53 such babies, with 36 or 67.9 per cent in Group I; and 17 or 32.1 per cent in Group II. Of the infants in Group II, the average number of normoblasts was 21.5, and for erythroblasts 3.0, giving a ratio of 7:1 as seen for premature infants.

As shown in Fig. 1, infants weighing over 5,000 gm. had an average of 32 nucleated erythrocytes, with a ratio of 7:1 (normoblasts to erythroblasts). While a diagnosis of prematurity in these infants (3 in number) may seem untenable, the maternal complications of diabetes mellitus, hydramnios, and multiparity, respectively are known to play a role resulting in infants of excessive size. Are they also premature?

weight in two months, and was discharged in two months as a living "abortion." The mother presented an unclassified toxemia.

The medicolegal value of the correct determination of maturity and prematurity in cases of disputed paternity, with known date of conception, and in posthumous infants, is apparent.

An average of four days was required for the disappearance of the nucleated red cells from the circulating blood. A decrease of 100 per cent was observed on the first day of life as compared with the cord blood. This same percentage reduction is seen in the comparison of the average number of nucleated erythrocytes in the 400 infants, namely 10 per 100 white cells, and the average figure of 5 as obtained by Vaughn on the first day of life. It was my impression from several smears made simultaneously from cord blood and from cutaneous puncture, that in the latter a lower percentage of erythroblasts was found. While the difference may be due to technical error, the erythroblasts being larger probably cannot pass easily through the capillary system.

In 6 cases of erythroblastosis fetalis, the maturation period ranged from three to eleven days, with an average of six days. This is one-third longer than the average of four days stated above. Since more erythroblasts are present in this disease, a longer time is required for maturation to the normoblastic stages. The premature infant with an increased number of normoblasts, requires less time for the evolution into the nonnucleated erythrocyte. Consequently, the hematologic diagnosis of erythroblastosis and prematurity may be made most accurately from the cord blood at the time of birth.

The ratio of erythroblasts to normoblasts may be of value in the determination of prematurity, in addition to the actual increase in the number of nucleated red cells. This ratio was observed to be about 6:1 for premature infants, and from 10:1 to 14:1 for mature infants. A ratio of about 3:1 has been observed in 3 cases of erythroblastosis fetalis, which is interpreted as evidence of prematurity for this disease. Apparently the nearer the period of conception, the smaller the ratio of normoblasts to erythroblasts.

In the chorion, Stander states that blood formation can be determined in the third week. According to Arey, hemoblastic mesenchyme gives origin to megaloblasts. These primitive red blood cells are huge, having a basophilic cytoplasm, since hemoglobin is absent. Their nuclei are large, and have a lacey network, which contains several nucleoli. The megaloblasts are the precursors of procrythroblasts, and in turn erythroblasts. These cells are present in the circulation up to the second or third month of gestation, being gradually replaced by nonnucleated cells. Ryerson and Sanes observed that practically all of the erythrocytes were nucleated in early pregnancy, and that megaloblasts could be differentiated. From the third to seventh month, the liver, spleen, lymph glands, and other of the internal organs participate in blood formation, and foci of hemopoiesis are present in these organs. These foci as well as the circulating blood contain erythrocytic elements in various stages of maturation. Erythroblasts are smaller than the megaloblasts, but have similar characteristics. They mature into

either orally or rectally, morphine and scopolamine were found to have no direct or apparent influence. Detailed analysis is omitted for lack of space. The following factors, however, deserve brief consideration.

Toxemia.—The toxemias of pregnancy were classified according to the classification of Stander and Peckham. There were 72 cases or 26.1 per cent in Group I; and 34 cases, or 27.2 per cent in Group II; showing no appreciable difference.

Anemia.—Cell volume determinations at the onset of labor as suggested by Pastore averaged 37.4 per cent and 36.6 per cent for Groups I and II, respectively, showing no significant difference.

Placenta.—The average weight of the placenta in Group I was 650 gm., and 668 gm. for Group II; which seems to indicate that weight alone is not always a criterion for prematurity. Histologic studies were made of 134 placentas by Dr. Herbert F. Traut. Of 72 placentas in Group I, 2 or 2.7 per cent showed prematurity; while of 68 placentas in Group II, 8 or 12.9 per cent were premature. This is an increase of about 400 per cent for Group II.

DISCUSSION AND SUMMARY

Prematurity has been shown to be more evident in Group II, which consists of infants having 10 or more nucleated erythrocytes per 100 leucocytes. This was seen in a slightly lower average weight, length, and duration of pregnancy, as compared with Group I. The incidence of prematurity was 100 per cent greater in Group II. This group also showed prematurity of the placenta 400 per cent more frequently. The incidence of twin pregnancy was also greater in Group II. Of the infantile deaths in Group II, 100 per cent showed prematurity at autopsy.

The study revealed the need for different standards of weight, length, duration of pregnancy, and the number of nucleated erythrocytes, for the determination of maturity and prematurity in twin infants and negro infants.

The prediction of the degree of prematurity from the number of nucleated red cells may be inaccurate in certain cases, since each infant may have an individual variation from the average figures. Some infants had abnormally high numbers and were considered at term. However this increase may be interpreted as evidence of immaturity, at least of the hemopoietic system. Thirty-two per cent of the excessive sized infants were premature according to the blood smear; and 33 per cent of the infants considered premature were mature according to the blood examination.

Prematurity is frequently associated with hemorrhagic disease, erythroblastosis fetalis, and intracranial hemorrhage. Prematurity is also more frequent in twin pregnancy. It is also associated with increased morbidity and mortality rates. Therefore accurate diagnosis of maturity and prematurity should be made in each infant from the standpoints of weight, length, duration of pregnancy, number of nucleated erythrocytes, histologic examination of the placenta, and x-ray studies of the ossification centers after the method of Adair. This will also aid in prognosis, and in the clinical management of the infant. This may be illustrated by a 1,400 gm. infant, 41 cm. long, of thirty-two weeks' gestation, who had only 6 normoblasts per 100 white cells. This infant doubled its

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THE EFFECT OF CALCIUM UPON UTERINE CONTRACTIONS AND UPON THE UTERINE RESPONSE TO INTRAVENOUSLY INJECTED OXYTOCICS

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THE literature on the relation of calcium to uterine contractility is not in agreement. In 1909 Blair Bell and Hick[1] reported in vivo experiments in which the administration of calcium as $CaCl_2$ caused marked contractions of the uterus of the pithed rabbit. In 1915 Blair-Bell[2] cited other work which led him to the conclusion that a reduction of the calcium content of the blood below an optimum level might be a factor in the causation of "primary uterine inertia"; he therefore advised the administration of calcium during the last trimester of pregnancy as prophylaxis against uterine inertia. Since the appearance of his original paper, several articles have been written on this subject, some of which[3-5] confirm the oxytocic action of calcium, while others[6-9] contradict the observations of Bell. Our investigation of the subject was undertaken because of the disagreement on this rather important subject.

The most recent report upon this subject appeared while the present work was in progress. Schübel[10] found that the minimal effective dose of pitocin was considerably diminished by the previous administration of calcium. This observation is in accord with the results to be presented in this paper.

METHODS

Twenty-five post-partum dogs and 5 post-partum rabbits were used for this study. These were allowed to deliver their young spontaneously, and twenty-four to forty-eight hours later each animal was anesthetized with nembutal and the abdomen opened. For recording the tone and motility of the uterus the method of Rudolph and Ivy[11] was employed, in which a balloon is placed in each uterine horn. The balloons were appropriately inflated and connected to a manometer. In addition a specially constructed balloon was inserted through the vagina to the level of the

normoblasts, which are still smaller, have shrunken pyknotic nuclei, and a cytoplasm that is less basophilic, since hemoglobin is being acquired. Ultimately the nonnucleated erythrocyte is produced.

As term is approached, the internal organs diminish their hemopoietic activity, and the bone marrow gradually assumes the major role of blood formation. Hemopoietic foci may persist, especially in the liver, as shown by Ferguson in 6 of 9 premature infants. The circulating blood likewise shows a decrease in the number of immature erythrocytes. Mature infants have less than 10 nucleated erythrocytes, as shown in Group I, and of these, 20 per cent had none at all.

Maturation of red cells depends on intrinsic and extrinsic factors according to Strauss and Castle, who believe that the latter may be vitamin B_2. The infant is of course dependent on the mother for these substances. The increased number of nucleated red cells in the excessive-sized infants may have been produced by a deficiency of vitamin B_2 on the basis of excessive weight gain. This is not corroborated by the twins in Group I, whose aggregate weights were excessive, namely over 4,000 gm.; without an increase in the number of nucleated red cells.

Since the completion of this study, the blood smears of 9 twin infants and 50 single infants have been evaluated, and the diagnosis of prematurity or maturity was made. The clinical records of these infants were then reviewed, and the hematologic evidence was correlated with the weight, length, and duration of gestation. From these cases, and from the original 400 cases, the following conclusions were made:

CONCLUSIONS

1. Prematurity should be considered when a smear of cord blood has 10 or more nucleated erythrocytes per 100 white cells; a mature infant is likely to have less than 10.

2. Weight, length, and the number of nucleated erythrocytes are better indices of prematurity, immaturity, and maturity, than the duration of pregnancy.

3. Twin infants and negro infants should have different standards for maturity and prematurity than single white infants.

4. Approximately one-third of the premature and excessive-sized infants, and about one-fourth of mature infants according to standards of weight and length, showed evidence of immaturity or prematurity on blood examination.

5. Infants with congenital abnormalities had an increased number of nucleated erythrocytes, which was attributed to prematurity.

6. A gradual disappearance of nucleated red cells occurs within four days after birth. Therefore the hematologic diagnosis of prematurity and erythroblastosis may be made most accurately from the cord blood.

7. The number of erythroblasts and normoblasts, as well as their ratio, seems to be approximately proportional to the degree of prematurity.

8. Routine examination of the fetal blood of the placenta is a simple diagnostic procedure.

When this drug was administered in doses of approximately 10 mg. per kilo of body weight, a depression of contractions occurred as illustrated in Fig. 2. By varying the dose different degrees of depression of uterine motility were obtained.

When the activity of the uterus was augmented by an injection of calcium, the activity could be immediately antagonized or returned to normal by the injection of an appropriate amount of sodium hexametaphosphate. This is illustrated by Fig. 3. Of course, after calcium had been injected, a larger dose of sodium hexametaphosphate was required to depress uterine motility than when calcium had not been administered.

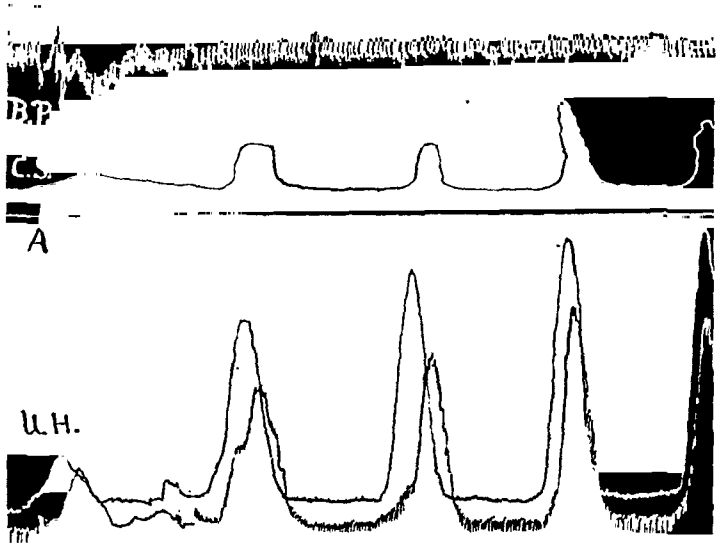


Fig. 1.—Showing the augmentation of uterine motility after calcium chloride (25 mg. per kilo) intravenously. *B. P.*, blood pressure; *C. S.*, record of the contraction of the cervical sphincter. *U. H.*, record of the contraction of the uterine horns.

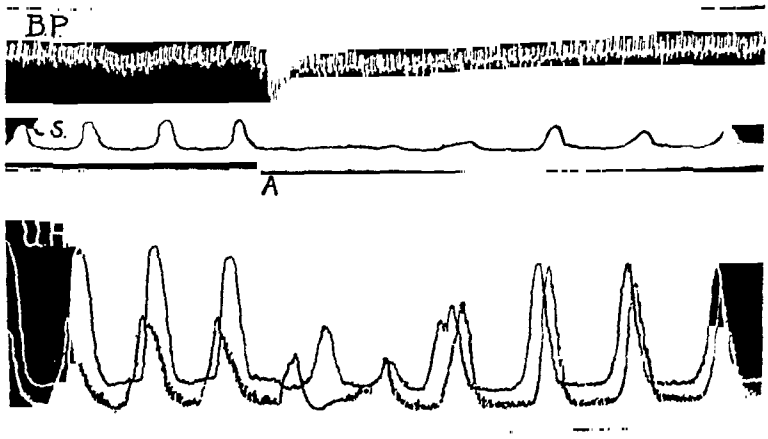


Fig. 2.—Showing the temporary depression of uterine motility by the intravenous injection of 10 mg. per kilo body weight of soluble sodium hexametaphosphate. In most animals a dose of 15 or 20 mg. caused an almost complete cessation of uterine contractions. *B. P.*, blood pressure; *C. S.*, cervical sphincter; *U. H.*, uterine horns.

The essential excitatory rôle that calcium plays in uterine motility is dramatically demonstrated by such an experiment. The results are as dramatic and almost as prompt as titrating acid against alkali. One who makes or observes such experiments cannot doubt the conclusions reached originally by Blair-Bell. In fact, the action of calcium and its antagonist, sodium hexametaphosphate, is so uniform on the post-partum dog's uterus in situ that the experiment makes a beautiful classroom demonstration.

cervical sphincter[12] for recording contraction of this structure. (The sphincter can be felt to contract on a finger placed in its lumen.) The abdomen was then closed with a continuous suture. The balloon at the level of the sphincter was connected to a Stoelting, aneroid-type tambour. Continuous records of the blood pressure were made with a mercurial manometer.

After the initial anesthetization, a basal anesthesia was maintained throughout the duration of the experiment by the subcutaneous injection of 1/15 to 1/5 gr. of morphine sulphate at intervals of one to two hours. This drug did not affect the uterine contractions significantly.

All of the test solutions were administered by the intravenous route. The calcium was administered as calcium chloride, in a solution such that 1 c.c. was equivalent to 30 mg. of calcium. The effect of this solution was first determined, and then, after the effect had subsided, the minimal effective doses (M.E D.) of pitocin (Parke, Davis & Co.), ergonovine (ergotrate*), and histamine (Pfanstiehl) were determined. These doses were then combined with calcium and tested.

The effect of soluble sodium hexametaphosphate, a drug (known under the trade name of Calgon), which counteracts the effect of calcium in the body, was determined, and then this drug was injected just before or along with pitocin, ergonovine, and histamine.

RESULTS

The results in both rabbits and dogs were essentially similar.

Normal.—Spontaneous activity of the uterus was recorded in all cases. The amplitude of contractions recorded on the tracing could be altered by increasing or diminishing the amount of air in the balloons, but once the proper amount of distention had been determined the contractions remained constant until some form of treatment was instituted. In most cases the cervical sphincter[12] was found to contract following the contractions of the horns; the height of the contraction of the sphincter occurred usually at the moment relaxation of the horns became complete. In some dogs the sphincter appeared to be coordinated with one horn, in others, the other horn. Variations in the same animal were not infrequent. In some cases the sphincter was found to contract irrespective of the activity of the horns, being apparently unrelated in any way to cornual activity. This was not usual in normal, untreated animals. The spontaneous motility of the uterine horns was like that reported previously.[11] In the dog the average rate of contractions was about 1 per four minutes. Between the contractions, which lasted for about one minute, both horns and sphincter were relaxed. The rate was considerably more rapid in the rabbit, an average of two full contractions occurring each minute.

The Effect of Calcium Upon the Post-Partum Uterus.—Calcium was administered in doses of 10 to 30 mg. per kilo of body weight. The essential effect upon the uterus was to increase both the tone and the rate and amplitude of contractions of both horns and cervix. This effect could be observed whether the uterus was quiescent or active. The effect was prompt, and sustained. The augmentation of activity was orderly and coordinated; spasm did not occur; slight tetany occurred in one out of 40 experiments. In one instance after contractions were inhibited by an overdose of nembutal, the administration of calcium caused an immediate return to normal rhythm. In two instances in which horns and cervix were incoordinated, the administration of calcium caused the appearance of absolute coordination. When the contractions were weak at the start of an experiment, or when they became weak after eight or ten hours of observation, the injection of calcium would frequently produce a dramatic improvement. This is illustrated by Fig. 1.

The Effect of Sodium Hexametaphosphate Upon the Post-Partum Uterus.—The injection of this drug, which combines with calcium and prevents it from manifesting its physiologic action, in adequate doses produced immediately complete quiescence even though the uterus had been extremely active prior to the injection.

*The ergotrate used in this study was generously furnished by H. W. Rhodehamel of Eli Lilly and Company.

larity between the two horns was usually not affected. In some instances the sphincter apparently did not react to this treatment at all, and was caused to become incoordinated with cornual activity. This was not the rule, however, and an increase in rate and amplitude of the cornual contractions was usually accompanied by a similar change in sphincter activity. The effect of histamine was prompt, and was observed to last for anywhere from four to twenty minutes. Thus, as might have been predicted from observations made on uterine strips, histamine increases uterine motility when given in doses that do not significantly alter blood pressure. Adair and Davis[15] found that the effects of histamine upon the human puerperal uterus were questionable. This, of course, does not mean that histamine in adequate dosage will not cause the human uterus to contract, since in the dog a somewhat larger dose can be used, and the recording apparatus is more sensitive.

The Effect of Pitocin, Ergonovine (Ergotrate) and Histamine When Administered With, or Directly After, the Injection of Calcium.—When these substances were administered directly after the injection of 20 mg. of calcium per kilo of body weight, the effect upon the uterus was invariably greater than that obtained from control injections. In most instances both rate and amplitude of contractions were affected, and the cervix and horns reacted alike. Thus, calcium not only augments

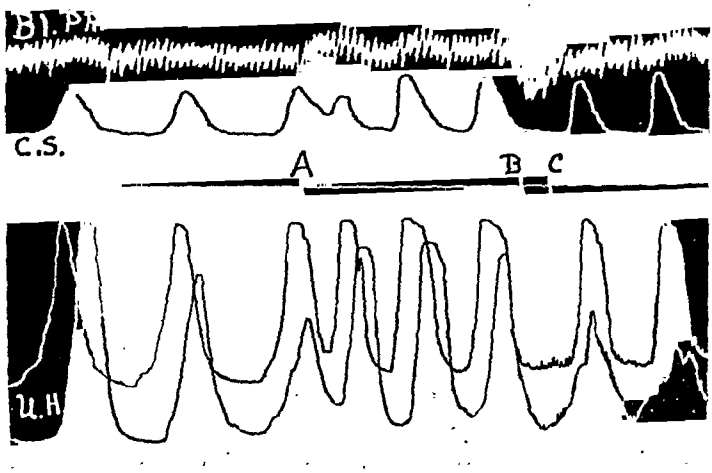


Fig. 4.—Showing abolition of the effect of pitocin on the uterus in situ by the injection of sodium hexametaphosphate. *A*, 4 c.c. of 1:100 pitocin intravenously; *B*, 27 mg. per kilo of hexametaphosphate; *C*, 4 c.c. of 1:100 pitocin; weight of dog, 18 kilo.

uterine activity by itself, but also potentiates the action of oxytocic drugs. Our observations regarding the role that calcium plays in determining the reaction of the uterus to pituitrin confirm those of Van Dyke and Hastings[5] on uterine strips.

The Effect of Pitocin, Ergonovine (Ergotrate) and Histamine When Administered Directly After the Injection of Sodium Hexametaphosphate.—When a preliminary injection of sodium hexametaphosphate was made, the effect of these drugs was considerably diminished. In some instances there was no perceptible effect from doses which previously had been shown to be definitely oxytocic. A minimum effective dose of pitocin, ergonovine, and histamine was annulled by an injection of sodium hexametaphosphate. Or, when the uterus was depressed by calcium want, the effectiveness of oxytocics was diminished.

The Effect of Sodium Hexametaphosphate When Administered Directly After the Injection of Pitocin, Ergonovine (Ergotrate) and Histamine.—As indicated previously, an augmentation of uterine contractions invariably followed the administration of pitocin, and ergonovine, the amount of augmentation being proportional to the dosage. In all instances following the administration of these drugs, the uterus could be depressed or rendered quiescent by the injection of sodium hexa-

The Effect of Pitocin Upon the Post-Partum Uterus.—In no instance was the untreated uterus refractory to this drug. Tetany and sustained spasm could be produced at will by the administration of sufficiently large doses. The minimum effective dose (M.E.D.) was found to vary in different animals from 1 c.c. of a 1:11,000 solution per kilo to 1 c.c. of 1:1,000 solution per kilo, given intravenously. When the minimum effective dose was administered to untreated animals, an increase in rate of contractions, and sometimes in amplitude, always followed. The contractions resulting were regular and showed no tendency toward incoordination or spasm. In some instances previously poor coordination was definitely improved. With the minimum effective dose the effect was usually transient and did not last more than from fifteen to twenty minutes. The cervical sphincter reacted as did the horns. The effect of pitocin was prompt and, if given immediately after a contraction, it generally caused another contraction before the usual latent period had expired.

The minimum effective dose of pitocin was determined for each animal because it was desired to determine the effect of calcium and sodium hexametaphosphate on the minimum effective dose of pitocin. These results will be mentioned later.

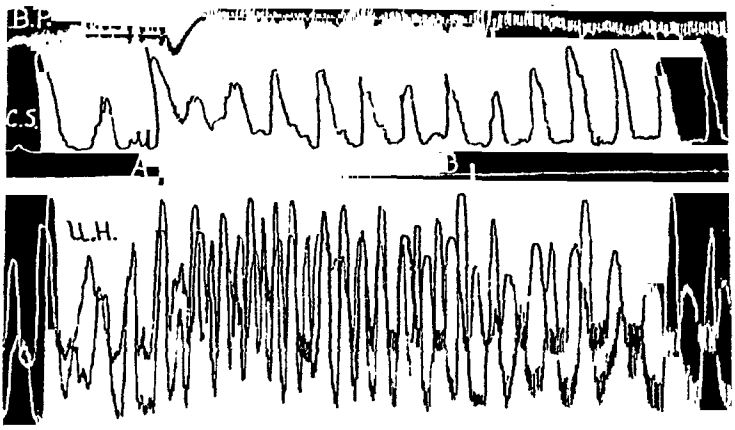


Fig. 3.—Showing a marked increase in the rate of uterine contractions caused by the intravenous injection of 15 mg. of calcium chloride per kilo at *A* and the depressing action of 10 mg. of sodium hexametaphosphate per kilo at *B*. *B. P.*, blood pressure; *C. S.*, cervical sphincter; *U. H.*, uterine horns.

The Effect of Ergonovine (Ergotrate) Upon the Post-Partum Uterus.—The effect of ergonovine on the motor activity of the uterus of the dog has not been studied. The effect of ergonovine was similar to that of pitocin, *except* that the maximal action often did not appear until as long as five minutes after the injection, and was usually maintained for a much longer period, in some instances for one hour or more. The minimum effective dose was found to vary from 1 c.c. of a 1:900 solution per kilo to 1 c.c. of a 1:100 solution. *Even in a dose as high as 1:10 in a 14 kilo dog, however, tetany and spasm of the uterus was not produced,* and only rhythmic contractions of increased rate and amplitude occurred. With still larger doses, prolonged spasm was observed only occasionally. These results on the dog confirm those for the human uterus as observed by Davis and others,[13] and Dudley and Moir.[14]

The Effect of Histamine Upon the Post-Partum Uterus.—The effect of histamine on the post-partum uterus of animals has not been studied. Histamine was administered in doses of 0.0081 mg. of the acid phosphate per kilo of body weight. This dosage was found to cause a barely perceptible change in blood pressure.

The administration of histamine in this dosage was followed, in most instances, by an increase in both rate and amplitude of contractions. Coordination and regu-

motility during labor. Winkler[17] reports a decrease in the calcium percentage of the dry weight of the uterus at term but, paradoxically, he finds the irritability of the uterus to be increased by the administration of calcium. The findings of Stander[18] are interesting in this regard, especially since it is well known that (a) calcium is soluble in an acid medium and relatively insoluble in an alkaline one, and (b) calcium is mobilized from the bones in the presence of a diminished alkaline reserve. This author reported a markedly decreased CO_2 combining power (a relative acidosis) in women at term. Bussabarger, Freeman, and Ivy[18] attribute rarefaction of the bones of gastrectomized puppies partly to a relative postcibal acidosis, because an acidosis tends to mobilize calcium from the bones. If these observations are applicable, one is led to the attractive hypothesis that the increasing irritability and reactivity of the pregnant uterus are at least partially dependent upon the ionic calcium content of that organ in relation to other ions such as potassium, and that progressive ionic changes occur in the uterine musculature until the ionic concentration is optimal for the uterine response to those factors which ultimately precipitate parturition.

The observations made suggest several possibilities for clinical application. It has been shown that in every instance where the available calcium was sufficiently reduced all motility stopped, and the uterus was entirely refractory to drugs which had been shown previously to be oxytocic. This finding is significant in that it may provide an explanation of those rare instances in which the postpartum uterus appears to be refractory to oxytocics, and points to a possible means of alleviating such conditions. Also, since uterine irritability is decidedly reduced by the lowering of available calcium, it seems rational to advise the use of phosphates and possibly alkalies in conditions where the uterus appears excessively irritable, as in threatened abortion, or in tetany. Further, there is the indication that the efficiency of the commonly used oxytocics may be increased by their combination with calcium. It should be pointed out that these latter possibilities are merely assumptions based upon animal studies, and their investigation in the human being is beyond the scope of the present work.

CONCLUSIONS

1. Calcium is necessary for the maintenance of the tone, contractility and coordinated activity of the post-partum uterus of the dog and rabbit. When the available calcium is sufficiently reduced by the use of soluble sodium hexametaphosphate, uterine contractions do not occur.

2. The oxytocic action of pitocin, ergonovine, and histamine is potentiated by calcium.

3. Doses of pitocin, ergonovine, and histamine, which are normally adequate for a uterine response, are ineffective when the available calcium is diminished.

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metaphosphate. The same was true in instances in which augmentation followed the injection of histamine. An illustration of the abolition of the pitocin effect by sodium hexametaphosphate is shown in Fig. 4.

Guinea Pig and Rabbit Uterus in Vitro.—Five guinea pigs in dioestrus and four rabbits which had been isolated for two months were used for this part of the experiment. The uteri from these animals were placed in oxygenated Locke's solution at 39° C. The addition of calcium caused augmentation of the contractions. The addition of pitocin (0.1 to 2.0 units added to a 50 c.c. bath) also augmented the contractions. When the two were added to the bath simultaneously an additive effect was observed. When the uterus was bathed with oxygenated, calcium-free Locke's solution, pitocin in the doses given above either had no, or only a very slight, effect. These results confirm those of Van Dyke and Hastings,[5] and are illustrated in Fig. 5.

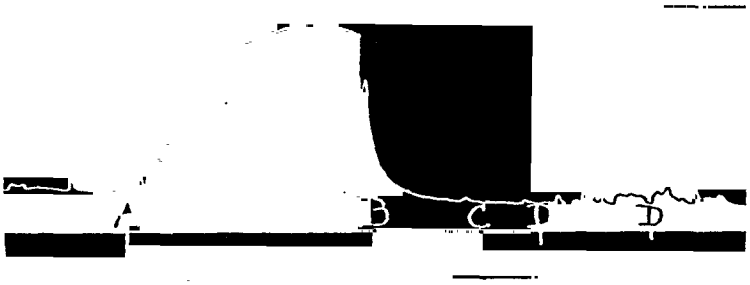


Fig. 5.—Showing the failure of the uterus of a rabbit to contract in response to pitocin when bathed by a Ca-free Locke's solution. *A*, 2 units of pitocin added to a 50 c.c. bath containing "normal" Locke's solution; *B* and *C*, uterus washed and bathed with Ca-free Locke's solution; *D*, addition of 2 units of pitocin, no response.

DISCUSSION

Our observations clearly demonstrate that calcium plays an essential role in the motor activity of the uterine musculature. When not present in adequate amounts the uterine musculature is inactive or depressed, and is refractory to the common oxytocics.

These results raise several interesting questions regarding the fundamental nature of uterine contractions. It should be remembered that calcium ions are essential constituents of all living tissue, and appear to play an important role in the permeability of the cell membrane. Soluble salts of calcium have a decided depressor effect upon striped muscle, but appear to stimulate or to be essential for the irritability of preparations of unstriped and cardiac muscle. Conversely, when the ionization of calcium is depressed by the administration of citrate or phosphate the irritability of striped muscle is increased, that of unstriped and cardiac muscle diminished. The findings which we have obtained indicate that not only is calcium concerned in determining the response of the uterus to drugs, and in the control of the irritability of the uterine musculature, but that in the relative absence of this element uterine muscle is incapable of contracting. This suggests the possibility that physiologic variations in the reactivity of uterine muscle (such as those occurring in pregnancy and at varying periods of the menstrual cycle) may result from physiologic changes in the availability of calcium ions.

In regard to the relation of this work to the problem of the onset of labor, it is well known that during pregnancy changes in calcium metabolism occur. However, relatively little satisfactory work has been directed toward a correlation of these changes with variations in uterine



B.

Fig. 1.—*A*, Left ureteroabdominal fistula. Pyeloureterogram showing solution retained in lower ureter at the site of injury. Treated by indwelling ureteral catheter. Healed in eight days. *B*, Retrograde pyelograms taken two years later showing normal left kidney and ureter. No obstruction to ureteral catheter at injured area.

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UROLOGIC COMPLICATIONS FOLLOWING COMPLETE AND SUPRAVAGINAL HYSTERECTOMY*

A Comparative Study

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LESIONS of the urinary tract are one of the commonest complications following removal of the uterus. Subsequent to Kennedy's excellent article in 1930 on "The Reconstruction of the Cervical Ligaments Following Complete Hysterectomy,"[1] the number of these operations on ward patients at the Woman's Hospital increased twofold. From 1922 to 1929 there were 223 total hysterectomies, whereas during the past eight years there were 438 of these operations. With the increase in this operation more urologic complications have resulted.

Some writers, notably Spencer of London, and to a certain extent Goodall, advocate routine complete hysterectomy; while others, although not conforming to this view, have for various reasons increased their indications for the total operation. There is, however, some discussion among gynecologists as to which course to follow. It is the purpose of this paper to present a comparison of the urologic complications following each type of operation. As far as the urinary tract is concerned, it is hoped that these results may prove that routine complete hysterectomy has disadvantages.

Included in this series were the supravaginal and complete hysterectomies that were performed on ward patients at the Woman's Hospital during the past eight years, excluding however operations for carcinoma. The principal indications for these operations were uterine myomas, ovarian cysts, extensive tuboovarian disease and serious pathologic lesions of the cervix. The operations were performed by 17 members of the hospital staff, some of them by the resident staff under supervision.

*Read at a meeting of the Gynecological Section of the Academy of Medicine, February 22, 1938.

infections in either group regarding the urinary findings, the temperature rise, the duration of the disease, and the treatment required or the degree of hospitalization.

In the supravaginal series there were 13 (27 per cent) late infections as compared with 10 (21 per cent) in the total hysterectomy group. In 6 of the 13 infections following the subtotal operation ureteral catheter drainage from four to fifteen days was necessary, whereas it was not required in any of the late infections following the total operation. The late infections subsequent to supravaginal hysterectomy were more severe than those after complete hysterectomy. The patients had an average higher temperature of one and one-half degrees, the duration of the infection was six days longer and the average time in the hospital five days greater.

COMPLICATIONS FOLLOWING SUPRAVAGINAL HYSTERECTOMY

In this entire group there were only three ureteral traumatic complications. The bladder was accidentally opened while separating it from the anterior surface of the uterus in two patients. In each case the injury was immediately recognized and repaired, and it healed without further trouble.

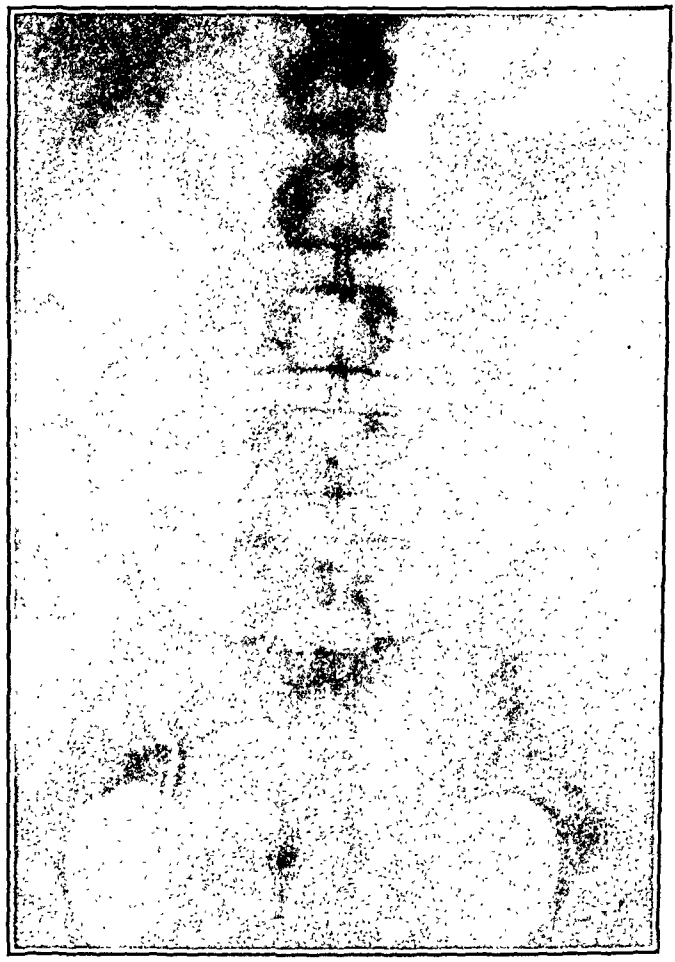


Fig. 3-A.

Fig. 3.—*A*, Left ureterovaginal fistula. Intravenous pyelogram shows left hydronephrosis because of ureteral injury. Patient cured of urinary leakage by destroying function of left kidney with x-ray. *B*, Intravenous pyelogram showing no function of left kidney following x-ray therapy.

The most serious complication was a left uretero-abdominal fistula. In this case (Fig. 1) the operator suspected he injured the ureter when he ligated the uterine artery. Within twenty-four hours there was urinary drainage from the abdominal wound. Cystoscopy was immediately performed and fortunately it was possible to pass a No. 5 ureteral catheter by the injured area in the ureter. This catheter was

All of the complications in this group of cases were studied cystoscopically and only those unquestionable acute renal or ureteral infections were included. Those infections that were accompanied by other complications such as infected wounds, definite pelvic inflammation, phlebitis, etc., were excluded.

RENAL INFECTIONS FOLLOWING COMPLETE AND SUPRAVAGINAL HYSTERECTOMY

In the series of 1,229 supravaginal operations 47 (3.8 per cent) were complicated by an acute postoperative pyelonephritis. Following 438 complete hysterectomies there were 47 (10.7 per cent) acute renal infections or three times as many as in the previous series.

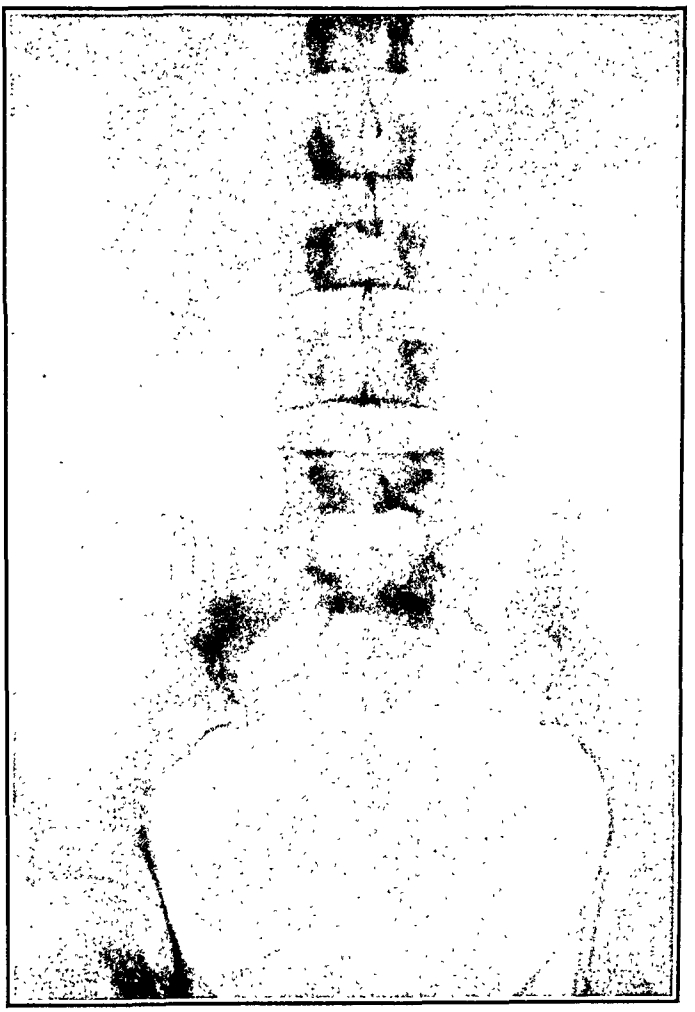


Fig. 2.—Left ureterovaginal fistula. Intravenous urogram showing ureter injured close to bladder with dilatation of left ureter above site of injury.

Although these infections may begin at any time after operation, in this series they commenced, on an average, either early, from the fifth to the seventh postoperative day, or late, from the twelfth to the fourteen day after operation. Subsequent to the supravaginal operation 34 (73 per cent) of these infections started from the fifth to the seventh day, whereas after the complete operation 37 (79 per cent) began at this time. There was no appreciable difference in the early

The third ureterovaginal fistula followed an operation for advanced tuboovarian disease and retroversion. This patient first noticed leakage of urine eleven days after operation. Cystoscopic study showed the fistula in the left ureter and there was also an acute infection in the kidney on that side for twenty-two days. She was observed in the follow-up clinic for several months but refused to enter the hospital for repair of the fistula and has not returned for further treatment.

The fourth patient's fistula (Fig. 3) resulted from an operation for fibroids the size of a four and one-half months' pregnancy. She leaked urine ten days after operation and cystoscopy six days later revealed a left ureterovaginal fistula. Her urinary drainage continued for several months but because she was a poor operative risk the function of her left kidney was destroyed by x-ray therapy. Ten months after operation the urinary leakage had stopped.

The right ureter was divided in 3 patients. In 2 of these cases the injury occurred while removing an intraligamentous myoma. It was recognized at once and immediate ureterorrhaphy was done. In the third case (Fig. 4) the injury resulted from a very difficult operation for adnexal disease. It was located close to the bladder so that the ureter could be easily transplanted into that organ. These 3 patients had an uneventful postoperative recovery.



Fig. 4.—Right ureter divided while removing intraligamentous myoma. Immediately transplanted into bladder. Intravenous urogram shows only slight dilatation of right ureter and renal pelvis. Good kidney function.

There were 3 vesicovaginal fistulas in this series, and they all followed operations for uterine fibroids. Two appeared on the fourth postoperative day and 1 eighteen days after operation. Within four months all 3 patients were operated upon and cured of their fistulas.

Three patients were readmitted to the hospital with an acute pyelonephritis. Two of them were admitted eleven and fifteen days after leaving the hospital while the third entered the hospital six and one-half months after operation. Except for evidence of renal infections the cystoscopic examinations were all normal.

allowed to remain in the ureter for seven days during which time the leakage of urine diminished. Eight days after operation a No. 6 catheter was easily passed up the left ureter and from this time on there was no urinary drainage from the abdominal wound. Cystoscopic study two years later showed a normal ureter and kidney.

COMPLICATIONS FOLLOWING COMPLETE HYSTERECTOMY

In this series also the bladder was accidentally opened twice but was immediately repaired and healed without further symptoms.

There were 10 serious urologic complications in the total hysterectomy group. Four patients had left ureterovaginal fistulas. One of them followed a very difficult operation for the removal of a malignant intraligamentous ovarian cyst. This patient first observed urinary leakage from the vagina thirteen days after operation. The next day a diagnosis of a left ureterovaginal fistula was made by cystoscopic study and intravenous urograms demonstrated a marked left hydronephrosis and hydroureter. This patient was cured of her fistula two months later by nephrectomy.



Fig. 3-*B*.

The second ureterovaginal fistula (Fig. 2) resulted from an operation for extensive tuboovarian disease. This patient first noticed leakage of urine eleven days after operation. Urologic study demonstrated only moderate damage to the left kidney and therefore, three months later, the ureter was transplanted into the bladder. She died of peritonitis four days after operation.

DISCUSSION

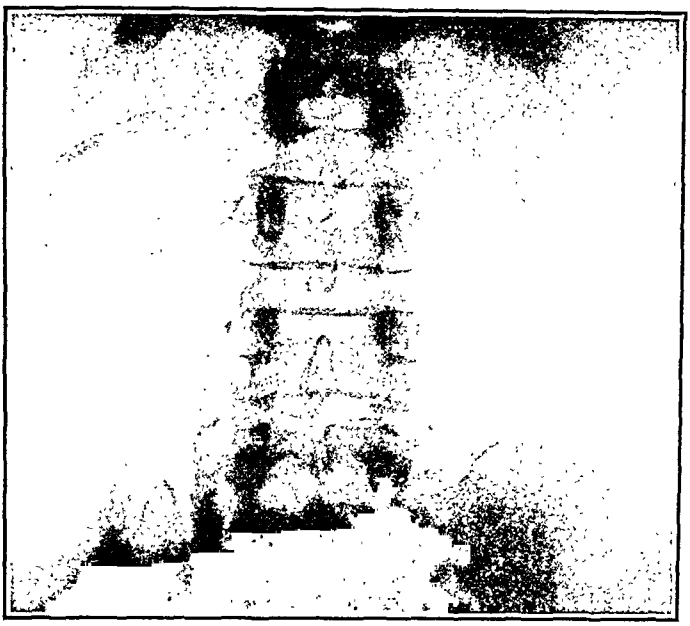
It is true that some of these injuries might have occurred if only a supravaginal operation had been performed. It might have happened to the two patients whose ureters were divided while removing intraligamentous tumors or to the two patients who had ureterovaginal fistulas following removal of a malignant ovarian cyst in one case and a large myoma in the other. As a rule, however, ureteral injuries that occur during a supravaginal hysterectomy are often recognized during the operation, whereas ureteral and also bladder injuries that follow the total operation usually go unrecognized and may result from necrosis due to interference with the blood supply of these organs. Despite the fact that these injuries might have followed the supravaginal operation all of these patients had a complete hysterectomy and they are included in that group.



Fig. 6-*A*.

Fig. 6.—*A*, Division of right ureter during hysterectomy. Immediately repaired. Intravenous urogram showing inhibition of function of right kidney for four weeks. *B*, Intravenous pyelogram five weeks after operation showing return of function to right kidney but some dilatation of pelvis and ureter.

As previously stated the late infections following supravaginal hysterectomy were more serious than those resulting from the total operation. Why is this so? The only apparent explanation is that it is the result of inflammatory obstruction of the ureter due to infection from cutting across the cervix or from the retained cervical stump.



A.



B.

Fig. 5.—*A*, Unsuspected injury to right ureter during supravaginal hysterectomy. Injury discovered because patient developed infection of kidney which necessitated cystoscopic study. Pyelogram shows sharply angulated right ureter. Ureter probably ligatured. *B*, Pyelogram showing dilatation of kidney and ureter following such an accident.

fistula. In this event nephrostomy may temporarily preserve the function of the kidney. Then, at a later date, the ureter may be transplanted into the bladder or bowel. If grave damage to the kidney has resulted from the fistula, nephrectomy will be necessary.

There may be some impairment of renal function following ureterorrhaphy. One patient in this series (Fig. 6) who had ureterorrhaphy showed inhibition of the renal function on that side for more than four

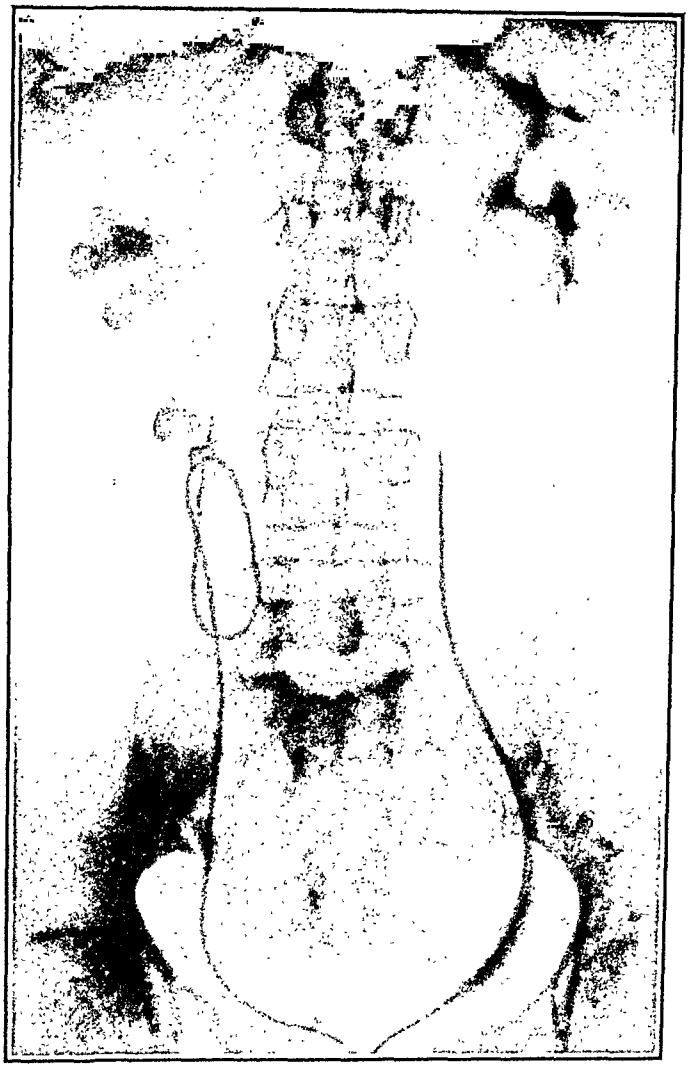


Fig. 7.—Ureter crushed by ligature during hysterectomy. Ligature removed. Cystoscopy shows large hydroureter and hydronephrosis probably because of edematous obstruction at site of injury.

weeks afterward. This resulted in a hydronephrosis which was caused by inflammatory swelling of the ureter at the site of the ureterorrhaphy. To anastomose the ureter over an indwelling ureteral catheter would tend to preserve the kidney function. In another patient (Fig. 7) whose ureter was crushed by a ligature a similar situation arose which caused a marked hydroureter and hydronephrosis. In this case, also, ureteral catheter drainage would have been advisable.

It is well known that hydronephrosis may be caused by transplantation of the ureter into the bladder as happened in one case in this

The majority of these injuries occurred previous to 1936 so that from now on, as our experience increases, the results will be better. On the other hand, even the most expert operators will occasionally injure the ureter, because, as set forth by Bonney, "The position of the ureter is so variable in pelvic surgery." Bland states "Despite the prevailing belief that ureteral injury is rare, I believe it to be one of the most if not the most frequent as well as the most serious accident in pelvic work." Undoubtedly ureteral injuries sometimes pass unsuspected. There may be no symptoms of ureteral injury. The first indication of injury, according to Eddy and Miller, "May be anuria, hematuria or the appearance of a fistula." Even these symptoms may be absent. The

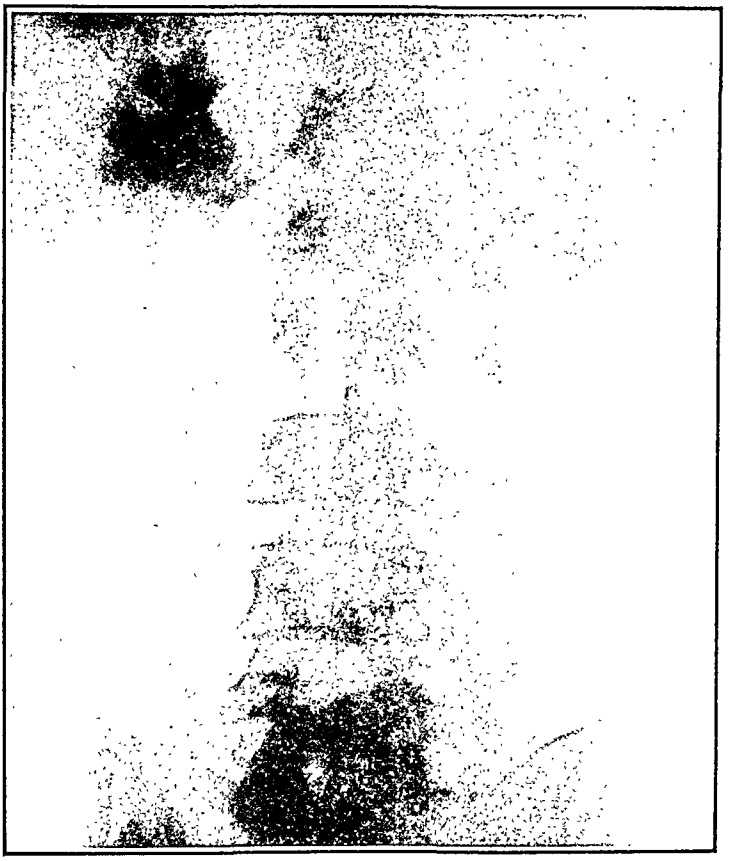


Fig. 6-*B*.

patient may develop an acute renal infection while in the hospital and the injury be observed when she is cystoscoped (Fig. 5). Harris and Brunton state that "The effects of ureteral injury may not be observed for months or even years after operation." As in this series, some patients may develop an acute infection of the kidneys, long after operation while others complain of various urinary symptoms for a considerable time. Certainly these complications must have some relation to bladder or ureteral trauma and all of these patients should have the benefit of a cystoscopic study.

Some ureterovaginal fistulas will heal spontaneously but the majority require operative treatment. Before the patient is ready for another operation, however, considerable renal damage may be caused by the

A CRITIQUE OF THE FACTORS INVOLVED IN CESAREAN SECTION MORTALITY*

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THE use and abuse of cesarean section and its place in obstetric surgery have given rise to controversy almost since cases involving this procedure have been recorded in medical literature. During the past decade this dispute has gained impetus from the searching surveys concerning maternal mortality in general which have been carried on by obstetricians in this and other countries.

Many case series have been collected either from the larger clinics or from the studies of maternal welfare committees in cities, sometimes in states. From an analysis of these statistics it has been shown that the maternal mortality following the cesarean operation throughout the United States is 5.8 per cent, while the infant is lost in 8.5 per cent of all cases. Inasmuch as an almost 6 per cent mortality is far higher than that following comparable abdominal operations for other conditions, as for example, hysterectomy for fibroids, it has been properly felt by the profession that abdominal hysterotomy is all too often selected as a method of delivery and that the indications for its use have been broadened unwarrantably. Lynch collected the data relating to 524,117 births from various cities and states from 1930 to 1935, and found an incidence of cesarean sections of 2.5 per cent. When closely scrutinized, these figures all seem to contain a considerable factor of error. In many of the series quoted, the incidence is based upon hospital deliveries alone, which obviously does not reflect the true condition. Thus, for example, the Committee on Maternal Welfare of the Philadelphia County Medical Society in its study of maternal mortality during the years 1931, 1932, and 1933 published the cesarean section statistics of the hospitals of the city in these years. There were 68,733 hospital deliveries with a cesarean section incidence of 2.6 per cent, but without exception all of the cesarean sections done in the entire city during this period occurred in hospitals.

The total urban births for the same time were 99,579, among which were 1,775 sections, giving an incidence of the operation in relation to the total births in the area considered of 1.78 per cent, rather than the 2.6 as commonly stated.

However, it is not with the frequency with which hysterotomy is invoked that I take issue but with the statements as to the mortality consequent upon the operation. The actual number of deaths and their relative total births are unquestionably accurate, and it is not the figures which I challenge, but the deductions drawn from them.

*Read at a meeting of the Detroit Obstetrical and Gynecological Society, March 7, 1938.

series. Hydronephrosis may also result from vesicovaginal fistulas. Those fistulas which follow complete hysterectomy are inaccessible, extremely difficult to cure and may require many operations.

From this study too, we have found that acute postoperative pyelonephritis, although three times more frequent following complete hysterectomy, is not as serious an infection as that which develops after the supravaginal operation.

In this series of cases ureteral and bladder injury was ten times more frequent following complete hysterectomy. The most serious of these injuries were the four ureterovaginal fistulas. They resulted in one death, one nephrectomy, the function of one kidney destroyed by radiotherapy and one patient who, although she could not be traced, would probably require nephrectomy in order to be cured. The seriousness of unrecognized ureteral injury with late renal complications cannot be minimized.

All of these patients were operated upon by well-trained surgeons in an outstanding hospital. Under these conditions and from the urologic viewpoint, the greater frequency of ureteral and bladder injury following complete hysterectomy, should make one hesitate before adopting this operation as a routine.

One may conclude therefore that routine complete hysterectomy is not advisable because of the greater frequency of urinary infections and ureteral and bladder injuries.

I wish to express my appreciation to Dr. Albert H. Aldridge for his valuable suggestions, to Dr. Henry G. Bugbee for the privilege of making the urologic studies and to Dr. George Gray Ward for the opportunity of presenting this paper.

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Murray, E., and Herrnberger, K.: The Functional State of the Vaginal Mucosa following Extirpation of the Uterus and Ovaries, Arch. f. Gynäk. 167: 167, 1938.

The authors show in a series of 46 women that ovarectomy stops growth as well as the normal rhythmic changes of the vaginal mucosa. Ovarectomy with preservation of the uterus stops only the cyclic changes. Hysterectomy with ovarian conservation causes rhythmic changes which one month later give the vaginal mucous membrane the same appearance as that found during pregnancy. This is probably due to a persistent corpus luteum. Ovarectomy combined with hysterectomy produces no changes for about six weeks, after which the vaginal epithelium undergoes a progressive and finally complete atrophy. Following radiation castration, no changes can be found for about 4 months. The vaginal epithelium following castration responds readily to stimulation with estrogenic hormones and those cases which showed the most marked postoperative atrophy responded the best to hormonal stimulation. The resulting hypertrophy always is very marked. Cessation of hormonal stimulation results in further retrogression and atrophy.

Ralph A. Reis

bearing upon the choice of abdominal versus vaginal delivery, both as regards the obstetrician and the patient.

It is my opinion, often expressed, that in women with manifest though not necessarily insuperable disproportion, whether this be of maternal or fetal origin, elective cesarean section under local anesthesia and preferably without a preliminary test of labor, offers the best prognosis for the life and well-being of the infant as well as the subsequent health of the mother.

If one contrasts the end results of such section with those following difficult forceps delivery or version, with their constant threat of fetal intracranial hemorrhage, Erb's paralysis and the like, not to mention the permanent and often irreparable damage done to the pelvic fascias and the sacroiliac articulation of the mother, the conclusion is inevitable that hysterotomy is the procedure of choice.

The matter of the test of labor is still unsettled. Highly regarded in many clinics it is rarely utilized by the writer, who confesses to a prejudice against the procedure. If a reasonable test of labor terminates in a spontaneous or low forceps delivery, it is obvious that the obstetrician who has been considering the possibility of section in such a case has been in error as to his findings. On the other hand, all too frequently tests of labor result in dystocia requiring ultimate abdominal delivery after the patient is exhausted, the membranes ruptured, and the golden moment of election has been lost.

It is my belief that the best plan is for the obstetrician to study each patient carefully to determine finally, during the last month of pregnancy, whether the labor will proceed normally or whether severe dystocia is likely to occur. If so, he should decide upon his course of action and having determined upon it, proceed either by elective cesarean or not, as his findings indicate.

This places the responsibility for the welfare of the patient squarely upon the shoulders of the medical attendant, where it belongs. If he be a competent and trained man, his percentage of error will be small indeed.

Now to return for a moment to the question of mortality statistics as affecting the decision of doctor and patient as to whether or not abdominal hysterotomy is to be employed to effect delivery.

Assume that a young woman engages an obstetrician for her forthcoming delivery. On investigation the pelvis is found to be definitely contracted, though not to an extensive degree. As term approaches, the infant is noted to be of average or greater size and engagement does not occur satisfactorily. Abdominal hysterotomy of the elective type is suggested by the obstetrician and the patient and her husband request information as to the relative risks of abdominal versus difficult vaginal delivery.

The mortality of cesarean section according to 17 American authors as quoted by Irving runs from 1 to 8 per cent, the average for 11,491 cases being 5.8 per cent. (In the clinic of the writer at Kensington Hospital

In recording maternal deaths following any form of vaginal delivery, it is customary to list the mortality according to the cause. Thus deaths from eclampsia, abruptio placentae, puerperal sepsis, etc., are so catalogued, *unless* the patient undergoes a cesarean section as a method of treatment, when, should a fatality eventuate, it is at once put down as a cesarean death, the underlying cause being ignored.

For example: two women suffering from central placenta previa with massive hemorrhage are admitted to the hospital at the same time. Both are given supportive treatment, preliminary blood transfusion and the like. The obstetrician in charge of one of these patients attempts delivery by Braxton Hicks version and as a result the woman dies. The case goes on record as one of placenta previa, the version being purely secondary and considered as contributory to the fatal result. The other woman is delivered by cesarean section and also dies. This case is instantly listed as a cesarean section mortality and so appears upon the records and the group statistics without any qualifications as to the true cause of the death.

An event occurring on my service at the Philadelphia General Hospital very recently, sharply emphasized this point.

A woman was admitted in shock, with the history that forceps delivery had been attempted unsuccessfully by a private physician. A diagnosis of probable rupture of the uterus was made, and after transfusion, laparohysterotomy was performed. The uterus was found to be the seat of an extensive incomplete rupture, its cavity filled with blood and after extraction of the infant hysterectomy was performed. The patient did not survive the shock and trauma, and in the next series of case analyses appearing, this hospital will be charged with one more cesarean death, though the circumstances leading to the choice of this procedure for delivery will not be mentioned.

In order to present a clear picture of the results of abdominal hysterotomy it is necessary to return to the older classification of the elective cesarean section and the section of necessity.

In cases of the latter group, comprising as it does, all those instances of neglected dystocias, women exsanguinated as a result of placenta previa or abruptio placentae, toxemia cases which have failed to respond to conservative treatment, the mortality must of necessity be high, in direct ratio to the resistance of the patient, the extent to which infection has progressed and so on.

In the first group, that composed of elective sections performed before the onset of labor, with intact membranes and chosen as a preferred method of delivery in women with contracted pelvis, patients known to have placenta previa without present hemorrhage, and other similar indications, the mortality should be exceedingly low, comparable to that following interval appendectomy.

Fatalities following the operation should only be due to those unsuspected accidents which are an unavoidable accompaniment to any intraperitoneal surgical intervention, thrombosis, pulmonary or cerebral, rarely peritonitis and still more rarely post-partum hemorrhage.

The importance of thus dividing cases of the cesarean operation, lies not merely in presenting a true statistical picture but has a direct

The third patient was admitted in shock and coma with a vague history of having passed no urine "for some time." The bladder was dry and the diagnosis of anuria with abruptio placentae was simple. A rapid hysterotomy was done, the placenta found entirely separated and the uterus filled with blood. The woman recovered from the operation and lived for six days with practically complete suppression of urine after which she died of uremia as proved by autopsy, at which time the uterus was found to be involuting well, the hysterotomy wound healing. Here again, I think, the method of delivery had no connection with the untoward result.

The fourth case was that of a patient suffering from advanced rheumatic heart disease, who entered the hospital moribund, not in labor and having had no prenatal care. Therapeusis directed to the cardiac lesion met with no response and at the request of the patient and her family cesarean section was done in the hope of saving the child, at least. The woman perished at the completion of the operation and the infant survived but a few hours. Here was possibly an unnecessary section but certainly it played no part in the unfortunate outcome.

It appears then that of the total of these deaths following section for all causes in this institution only one could reasonably be charged to the operation; all of which seems to bear out my view as to the necessity for classifying the indication for which the cesarean section is performed before determining its responsibility in the mortality rate.

Referring again to the figures already given for two clinics at Kensington and Chestnut Hill, there were in the past six years 137 cesarean sections with a maternal mortality of 2.91 per cent. Of these operations, all of which were performed by me or one of my associates, 124 were elective and 32 were operations of necessity; many of these were carried out among seriously ill women, neglected in labor, and in a number of whom craniotomy was probably the procedure of choice. This operation, however, aside from certain religious interdictions is extremely repugnant in the presence of a living child and certain patients were undoubtedly lost by reason of our aversion to craniotomy under such circumstances.

Among the 124 elective sections, there was no maternal mortality whatsoever and a surgical morbidity of something under 6 per cent.

Among the 32 operations of necessity, there were 4 deaths, or 12.5 per cent which have already been abstracted.

This summary supports the contention that the elective operation carries with it a fairly negligible risk whereas when enforced by some complication of labor the risk is great, but is generally justified by the fact that many of these women are doomed and the hysterotomy seems to offer them and their infants the most hopeful prognosis. Again as one recalls his experiences with this operation he must be impressed by the number of instances in which section performed with no hope of success has resulted in the uneventful recovery of mother and child. Such cases, surely, seem to counterbalance the deaths which occur as a result of its employment in cases where craniotomy or other procedures of vaginal methods of delivery might have been invoked.

From the above views concerning the value of cesarean section and the relatively great safety of the elective operations, it should follow that he who holds such opinions must necessarily perform many hysterotomies. In the combined clinics summarized in this paper, during the past six years there have been 8,528 deliveries with 137 sections or an

for Women and at Chestnut Hill Hospital there have occurred in the past six years 137 cesarean sections with a maternal mortality of 4 or 2.91 per cent.)

The only authoritative information, then, which could be given to the patient in question would be that her chances of death as a result of hysterotomy would be about one in twenty or slightly less. This constitutes a formidable mortality rate and any woman is entirely justified in refusing to accept so grave a risk to her life, when vaginal delivery offers so much the better prognosis, even at the possible expense of the infant.

That the above statements portray the true situation is manifestly untrue. What then is the death rate in purely elective cesarean sections, done before the onset of labor, preferably under local anesthesia, with intact membranes, no vaginal or rectal examination having been permitted within twenty-four hours of the operation?

I am not aware of any published series of such selected cases, but from my own experience, I am convinced that the risk is minimal, certainly well under 1 per cent and comparable to the death rate in interval appendectomies and other simple intraperitoneal interventions. In support of this statement there is a summary of my last 120 *consecutive elective* sections with no maternal mortality, a surgical morbidity of 6 per cent and a total infant loss of 2 or 2.5 per cent.

Incidentally, these infant deaths were unusual. The first occurred in a woman who had previously had two babies perish during the course of spontaneous labor and a third which died one week before term. In an attempt to secure a living child, elective section was proposed and accepted and although the hysterotomy went well under local anesthesia, the child did not breathe and heart action ceased a few minutes after delivery.

In the second case the baby cried lustily at birth but perished within twenty-four hours, apparently of some congenital cardiac lesion although autopsy was not permitted to confirm this.

After such personal experience, I have no hesitation in recommending the elective operation to my patients when, in my opinion, it offers the best hope of successful delivery, and in assuring the woman and her family that the risk to mother and infant is very small.

It has been stated above that in Kensington Hospital for Women and Chestnut Hill Hospital there were four maternal deaths following cesarean section and in view of the opinions expressed previously, in this paper, it is interesting to analyze these four fatalities.

One occurred in a woman who was subjected to classical section after a twelve-hour test of labor, without vaginal examination and eight hours after rupture of the membranes. She died of a fulminating peritonitis, the fatal outcome being obviously the direct result of the operation and chargeable to it alone.

The second case was that of a woman admitted exsanguinated after hemorrhage from a central placenta previa. She was moribund and the cervix was not sufficiently dilated to permit of Braxton Hicks version. The hemorrhage continued actively and a rapid hysterectomy was performed, fluids being given intravenously during the operation. The patient perished from shock and hemorrhage within an hour. In all fairness the woman was doomed before her treatment began and the hysterectomy was certainly only a minor contributory cause to the mortality, if indeed it played any part.

into the cervix finds its way almost immediately to the submucosal area in the trigon of the urinary bladder. This is evidence of the paths of infection. Furthermore, a cervix which grossly appears to be normal often becomes a source of infection following a subtotal hysterectomy, as a result of interference with its normal blood supply and also because of cessation of its normal physiologic action. It is therefore not uncommon to have to remove a retained cervical stump on account of its residual inflammatory character. For these reasons it becomes an increasingly difficult problem to say what patients should be treated by subtotal hysterectomy as it is impossible to determine whether or not a cervix will continue healthy.

Since a leiomyoma is the most frequent indication for hysterectomy and as the majority of the patients who have this type of tumor have had children, it is reasonable to assume that the cervix should be removed with the uterus more often than is being done in most clinics, because it is rare to find what is considered a normal cervix in the multiparous woman.

In order to avoid some of the technical difficulties associated with total abdominal hysterectomy, a subtotal abdominal hysterectomy has been substituted and the cervix is then coned out, cauterized or even repaired or amputated. None of these methods of handling the cervix affords much protection against the later development of cancer, and also numerous infected cervical glands are often opened or only partially destroyed; this leaves an infected tissue which is prone to heal slowly and irregularly. I have seen cases in which the external os closed early before the upper portion of the cervical canal had healed; this was followed by an abscess. The infection extends to the broad ligament and cellular tissue and, therefore, contributes to a prolonged convalescence and morbidity.

Leiomyomas are often degenerative in type, and there is not only chronic infection in the cervical tissues but also much edema of the broad ligaments and of the uterosacral and ovarian ligaments. This edema is a positive sign of danger in the surgical management of these tumors. It results from lymphatic obstruction secondary to chronic infection, and, unless these tissues are removed, cellulitis will follow too frequently. Edema is also frequently encountered during the course of hysterectomy for metritis and pelvic inflammatory disease. In conditions of this type which are of long duration the infection, which usually is streptococcal in type, extends to the lymphatics of the broad ligaments and to the lymph nodes along the iliac vessels and occasionally to the inguinal regions. Unless the extent of the infection is carefully estimated, a subtotal hysterectomy may be followed by an extensive cellulitis of the broad ligaments which involves the entire pelvic tissues. The convalescence is then prolonged from three to six weeks and the cervical stump becomes fixed, edematous and painful if it is touched. This sequence of events is most likely to follow retention of the cervical stump in postabortal infections which have a tendency to exacerbations following menstruation or trauma of any type. It also is characteristic of that group of cases in which surgical interference has been previously performed dur-

incidence of 1.6 per cent. This is well within the group of "low cesarean clinics" and emphasizes the statement that a strong prejudice in favor of cesarean section as opposed to difficult vaginal delivery does not imply its promiscuous employment, and here I venture to become personal and to state my obstetric credo, which is: That obstetrics should be practiced by trained obstetricians, versed in all the methods and maneuvers designed to facilitate childbirth.

And also, that the obstetrician should study each patient in detail and utilize, without hesitation, that method which in his considered opinion offers the greatest hope for a successful termination of the labor as regards both mother and child.

1814 SPRUCE STREET

THE POSITION OF TOTAL HYSTERECTOMY IN THE TREATMENT OF BENIGN AND MALIGNANT CONDITIONS OF THE UTERUS*

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TOTAL abdominal hysterectomy has in general been considered as a radical procedure and usually has been believed to be associated with a high mortality and high morbidity; therefore, it has been regarded as a dangerous operation. In view of this generally accepted opinion, I wish to consider some indications for total hysterectomy in benign and malignant conditions, as these indications seem to be sound and essential. The most frequent benign conditions of the uterus are leiomyoma, adenomyoma, and chronic pelvic inflammatory disease.

The decision as to whether a total or subtotal abdominal hysterectomy should be performed for benign conditions is determined principally by the condition of the cervix. In cases in which hysterectomy is contemplated the cervix should be carefully inspected and palpated. Cervical erosions and lacerations, endocervicitis, cystic cervicitis and polyps all indicate an unhealthy cervix. The external os may be firm and smooth and an active endocervicitis overlooked. Cysts situated in the cervical canal may extend to the internal os and each cyst may be infected. In cases in which cervical polyps tend to recur it has been observed that malignancy is very likely to develop later. Considerable research has demonstrated that the cervix is a frequent source of infection and that such infection has a definite relation to other infectious processes within the body, such as infections of the small joints, retinitis and choroiditis. There is a very definite relationship between infections of the cervix and infections of the urinary tract as some of the lymphatics of the cervix extend directly to the base of the bladder and also upward along the ureters and to the pelvis of the kidney. A suspension of graphite injected

*Read at a meeting of the Louisiana Obstetrical and Gynecological Society, New Orleans, Louisiana, May 2, 1938.

which is the only true supporting structure, can be shortened and reattached to the sides of the vaginal vault and will afford proper support to the vagina.

The surgical risk of total hysterectomy is considered to be greater in cases of malignant lesions of the fundus than it is in cases of benign conditions, but if the patients are selected carefully there need not be any appreciable increase in the risk. As a further protection against infection the vagina must be thoroughly cleansed as there always is a bloody discharge in the vagina for some time, and this often is more or less septic. The discharge not infrequently extends into the uterine cavity. The cervix should be firmly closed by sutures to prevent soiling or contamination or the occurrence of secondary implants at the time of hysterectomy. If hysterectomy is delayed a few days in order to determine the presence or absence of malignancy in the scrapings after fixation, the surgical risk is increased greatly owing to the spread of infection from the lesion, which is usually secondarily infected, to the broad ligaments, lymphatics, and peritoneum. There must be no delay, therefore, between the curettage and the hysterectomy.

Carcinoma of the fundus is a disease which appears during or after the menopause. However, should it develop during the reproductive period of life both adnexa should be removed without regard to the physiologic effect of castration as an adenocarcinoma of the fundus not infrequently extends from the fundus along the Fallopian tube to the ovary and peritoneal cavity. It is my custom, when operating in cases of carcinoma of the fundus, to place a clamp across the fimbriated end of each Fallopian tube as soon as the abdomen is opened. The fundus of the uterus is covered with a gauze sponge and held firmly with the hand and not with instruments. The involved tissues must be handled gently to prevent dissemination of any tumor tissue to the lymphatics and to avoid rupturing the uterine wall adjacent to the malignant lesion, where it is edematous and very friable.

There are some gynecologists who favor the intrauterine application of radium and deep roentgen therapy for carcinoma of the uterine fundus instead of total extirpation of the uterus and both adnexa. I cannot agree with them for very definite reasons. First and foremost, it seems to me that a malignant lesion anywhere in the body should be removed surgically if this can be done safely and completely. If women are to have carcinoma, the fundus of the uterus is one of the most favorable sites because this organ can be totally removed with a very low mortality. In about 90 per cent of cases of malignant lesions of the fundus, the lesions grow very slowly and the grade of malignancy is 1 or 2. They remain confined to the uterus for months and occasionally for years before they spread to other tissues. The longest duration of a carcinoma of the fundus in my experience was eight years. In about 10 per cent of cases the tumor grows rapidly, the grade of malignancy is 3 or 4 and the patients are in poor condition. Symptoms usually have been present for a short time and the patients rapidly show the effects of a highly malignant tumor just as do patients with highly malignant lesions anywhere in the body. The prognosis in such cases always should be guarded. At the

ing the subacute or early stage and in which residual infection manifests itself by pain, discharge, occasional fever, and disability. Under such circumstances total abdominal hysterectomy with removal of both adnexa is the safest procedure and gives the best assurance of complete restoration of health, because all tissues that are infected are totally removed and the lymphatic involvement subsides rapidly. I am sure that subtotal hysterectomy in this group of cases is potentially a more dangerous practice and has been followed by more complications and deaths than total removal of the uterus and adnexa.

Diffuse adenomyosis, or endometriosis, of the uterus, adnexa and the peritoneum of the cul-de-sac is more satisfactorily managed by total hysterectomy when removal of the uterus is advisable. In this condition all the pelvic organs are adherent in one mass and are somewhat fixed to the intestine. The ovaries consist of chocolate cysts and the entire mass is somewhat inflammatory owing to its proximity to the sigmoid colon and rectum. In mobilizing these structures there is considerable oozing of blood, which can be most adequately controlled by ligating all branches of the uterine artery to the cervix and lateral vaginal wall followed by total removal of the uterus.

The technical difficulty of total hysterectomy under any circumstances is perhaps greatest in this condition because it is necessary to visualize the ureters and elevate the base of the bladder from the cervix. The ureters are always involved in the endometrial process and are fixed to the tissues near the cervix. It has been my custom to identify the ureters and retract them laterally by means of a gauze tape. They can later be replaced behind the peritoneum during the final peritonization of the pelvic floor, without any subsequent injury. The function of such ureters was studied in a large series of cases following total hysterectomy for these conditions, by means of intravenous urography. The ureters were found to be in their normal situation and were not dilated. It was obvious, therefore, that the ureter could withstand considerable trauma without causing subsequent complications.

When the cervix and rectum are somewhat fixed, it is often advisable to follow the suggestion of Masson, who advised that the cervix be cut across just above the uterine vessels, then, while the cervical stump is held anteriorly by a tenaculum, the rectum is separated from the posterior wall of the cervix. The cervix is then split posteriorly, and it is easy to separate it from its vaginal attachments. In these cases the healing process and the subsequent freedom from pelvic pain are truly remarkable.

Subtotal abdominal hysterectomy is not infrequently performed for benign conditions associated with an elongated cervix or in cases in which there are excessive degrees of uterine prolapse and relaxation of the vaginal walls, which later result in prolapse of the cervical stump that will require surgical treatment. In such cases it is not possible to support the cervical stump adequately or properly from the abdominal side without extensive dissection or manipulation. However, if the cervical stump is removed at the time the uterus is removed, the broad ligament,

of the cervix are highly malignant lesions and extend early to contiguous structures, which makes it highly improbable that the entire growth can be removed. Also, in approximately 90 per cent of the cases the condition is inoperable at the first examination. Only about 5 to 10 per cent of the lesions have a low grade (Grade 1 or 2) of malignancy, and might be considered operable if the patients are observed early in the course of the disease. In such instances a more radical hysterectomy than the usual total abdominal hysterectomy is indicated. The Wertheim abdominal hysterectomy is usually employed; this consists not only of total removal of the uterus and adnexa but of removal of all the tissue within the broad ligaments and the upper 1 or 2 inches of the vagina. This procedure is unquestionably more difficult than the usual total hysterectomy and should be undertaken only by those who are completely familiar with the technic involved. At the Clinic our attitude with respect to surgical treatment of carcinoma of the cervix is illustrated by the fact that the condition was treated by operation in only 18 of a series of 717 cases. Six hundred and forty-two patients were treated by irradiation only, and 57 were treated by both operation and irradiation. More recently, some of the smaller lesions have been destroyed by irradiation, and six to eight weeks later a total abdominal hysterectomy is performed on the basis that the chances of cure may be increased by complete removal of the organ involved. Sufficient time has not transpired since operation to evaluate the results in the group of cases in which this method has been used.

Malignant lesions of the adnexa usually are encountered among patients who are more than thirty-five years of age, and the incidence is greatest in the fifth decade of life. The uterus may or may not be involved in the malignant process, but it may and often does contain benign lesions such as myomas and adenomyomas which necessitate removal of the uterus. The endometrium is occasionally the site of an independent malignant lesion in addition to that found in the adnexa. Malignant lesions of the ovary, such as papillary carcinomas and the solid carcinomas, become attached early to the peritoneum of the broad ligament and to the posterior surface of the uterus; therefore, if one expects to eradicate the malignant process it is necessary to remove the entire uterus as well as the adnexa. Furthermore, 50 per cent of malignant cysts affect both ovaries, and the effects of castration must be disregarded and a panhysterectomy must be performed in cases in which such lesions affect a young woman.

When malignant lesions of the adnexa involve the uterus, peritoneum, or omentum, the ultimate prognosis is poor but not entirely hopeless. These tumors have a peculiar characteristic, and this is especially true of the malignant cysts. Although they have extended to other organs, the secondary growths often subside or are held in check by removing the parent growth by a panhysterectomy and following this procedure with intensive irradiation.

The importance of total abdominal hysterectomy and removal of both adnexa in malignant lesions of the ovary and Fallopian tube when the lesion is operable cannot be overestimated. In cases in which one adnexa has been removed six or eight months previously because of a malignant

Mayo Clinic we supplement surgical removal with the application of radium therapy to the vaginal vault and roentgen therapy in front and back of the pelvic region as a postoperative measure. Some physicians advise a preoperative course of radiation therapy which is followed in six to eight weeks by a panhysterectomy. It will be necessary to evaluate the results of each method in five or ten years before it is safe to say which method of treatment results in the greater number of cures. Personally I feel that this small group of highly malignant lesions offers a good field for discussion, as the results of any method or combination of methods of treatment by different gynecologists at the present time are not what we would like to have.

From the evidence so far submitted by those who advocate radium therapy for all grades of malignant lesions of the fundus, I am convinced that for the large group of low-grade lesions at least, total abdominal hysterectomy with removal of both adnexa is the preferable method of treatment.

Each year at the Clinic we are seeing a greater number of patients who have pyometria and metritis as a sequel to the intrauterine application of radium for malignancy. The result of such treatment, as far as the patient is concerned, is equally as bad as the malignant lesion. Furthermore, it is impossible to convince the patient that the cancer has most likely been destroyed. Complete relief does ensue after a panhysterectomy has been performed, but the difficulty of the operation is increased by the contraction and fixation caused by the radium therapy.

In view of the fact that carcinoma of the uterine fundus usually occurs beyond the middle period of life, there will be some cases in which physical disability is a definite contraindication to any surgical procedure. For example, extreme obesity associated with cardiovascular disease and arteriosclerosis associated with anginal attacks and senility are certainly conditions that alter the surgical risk considerably. In such cases life expectancy is not great; therefore, the patients should not be subjected to any extensive surgical procedure for malignant disease.

In evaluating the results of the treatment of carcinoma of the uterine fundus by total hysterectomy only, by irradiation only or by a combination of both methods, we found that in the five-year period from 1925 to 1929, 251 patients with cancer of the body of the uterus were treated at the Mayo Clinic. Ninety of the patients were treated by operation only; 48 were treated by irradiation only and 113 were treated by operation and irradiation. In 70.4 per cent of cases in which the carcinoma was Grade 1 and was treated by operation only, the patients were living five or more years after operation. In the 113 cases in which cancers of Grade 2 or higher were treated by operation and irradiation, 63.8 per cent of the patients were living five or more years after completion of the treatment. Of the small group of patients who were either poor surgical risks or who were considered to have inoperable lesions, 22.5 per cent were living five or more years after irradiation alone.

In this country malignant lesions of the uterine cervix generally have been considered more amenable to irradiation therapy than to surgical removal of the uterus. The explanation is that 90 per cent of the cancers

A CRITICAL ANALYSIS OF BLOOD LOSS FOLLOWING DELIVERY*

With Special Reference to the Value of Ergotrate

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THE occurrence of an excessive blood loss during and after the third stage of labor might appropriately be termed, because of its serious consequences, Obstetric Enemy Number One, for no other accident or complication in obstetrics has such potential dangers or is encountered as frequently.

The present study is an investigation of the factors influencing blood loss in a series of 1,290 consecutive cases delivered on the Bellevue Obstetrical Service during the period from April, 1936 to April, 1937, with an additional report on 1,445 consecutive deliveries on the same service from April, 1937 to April, 1938. A brief preliminary survey has been made of the incidence and special causes of hemorrhage in order to gain an idea of the extent of the problem. The chief aim, however, has been to examine the effects of certain oxytocics upon the incidence and severity of post-partum hemorrhage.

The cases were consecutive except for the exclusion of patients delivered by cesarean section. The majority were delivered by an interne or medical student under the supervision of a resident, only the cases culminating in major operative procedures being directed by an attending obstetrician.

Five hundred cubic centimeters or more of blood loss has been, somewhat arbitrarily perhaps, considered by us to constitute post-partum hemorrhage. This method has the advantage of simplicity and general use, although it is perhaps less accurate than other criteria, taking into account the weight of the patient and the cell volume of the blood (Pastore). The data collected included notes on the "action of the uterus" and the measured blood loss during the third stage, with the delivery of the placenta and thereafter.

THE INCIDENCE OF POST-PARTUM HEMORRHAGE

There was a total of 136 cases classifiable as post-partum hemorrhage in the 1,290 studied, an incidence of 10.5 per cent, or when 600 c.c. is taken as the basis, 73 cases or 5.65 per cent. This compares favorably with the figures obtained by Williams of 19.5 per cent for the 500 c.c. criterion, and 13 per cent for the 600 c.c.; by Peckham of 6.1 per cent on the basis of 600 c.c.; and by Cragin, 10 per cent on

*Read before the Section on Obstetrics and Gynecology, New York Academy of Medicine, May 24, 1938.

lesion, it is common to find an inoperable lesion in the remaining ovary, and metastasis. The lymphatics of the adnexa are so intimately connected with those of the uterus that it is hardly reasonable to assume that the malignancy has not extended to the adjacent tissues of the uterus and broad ligament. Recurrence frequently is seen early at the site where the ovarian vessels were divided from their connection with the uterine artery. This is presumptive evidence that the malignant process, although it grossly appeared to be confined to the ovary, had in fact extended beyond the ovary. The result is so disastrous in such cases that I am sure the interest of the patient would be better served if panhysterectomy followed by irradiation were given more consideration.

SUMMARY

The uterine cervix is generally not normal in cases of leiomyoma of the fundus of the uterus, particularly if the patients are women who have had children. It also is difficult to estimate what cervices will remain free from infection subsequent to a subtotal abdominal hysterectomy. An infected cervical stump not uncommonly is the direct focus of infection in arthritis of the small joints, and in iritis, choroiditis, and myositis. It is difficult and frequently impossible to support a prolapsed or elongated cervix properly at the time a subtotal hysterectomy is done. In metritis and chronic pelvic inflammatory disease caused by low grade streptococcal infection, a diffuse pelvic cellulitis often occurs following a subtotal hysterectomy but is rarely a complication after total hysterectomy.

Ninety per cent of the carcinomas of the fundus are adequately managed by total abdominal hysterectomy alone or combined with irradiation. Operation will be contraindicated in a small group of cases as a result of other physical disabilities. In a very few cases of carcinoma of the cervix the Wertheim type of hysterectomy may be employed; these are cases in which the grade of malignancy is low and the patients are seen early in the course of the disease.

Total abdominal hysterectomy should be given greater consideration in the management of operable malignant lesions of the adnexa, and if the grade of malignancy is 2 or higher subsequent irradiation should be employed.

Cuthbert, J. C.: The Treatment of Urinary Infections in the Puerperium, Lancet 2: 720, 1938.

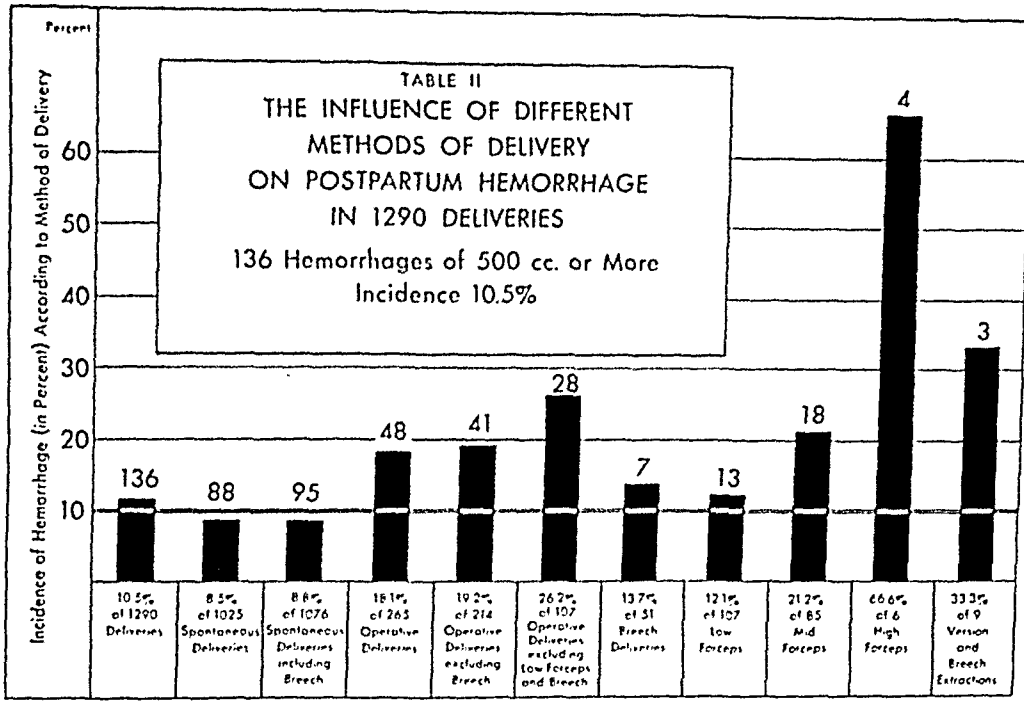
The author reports, from the Queen Charlotte's Maternity Hospital, 106 cases of puerperal urinary infection, most of them complicated by a genital tract infection.

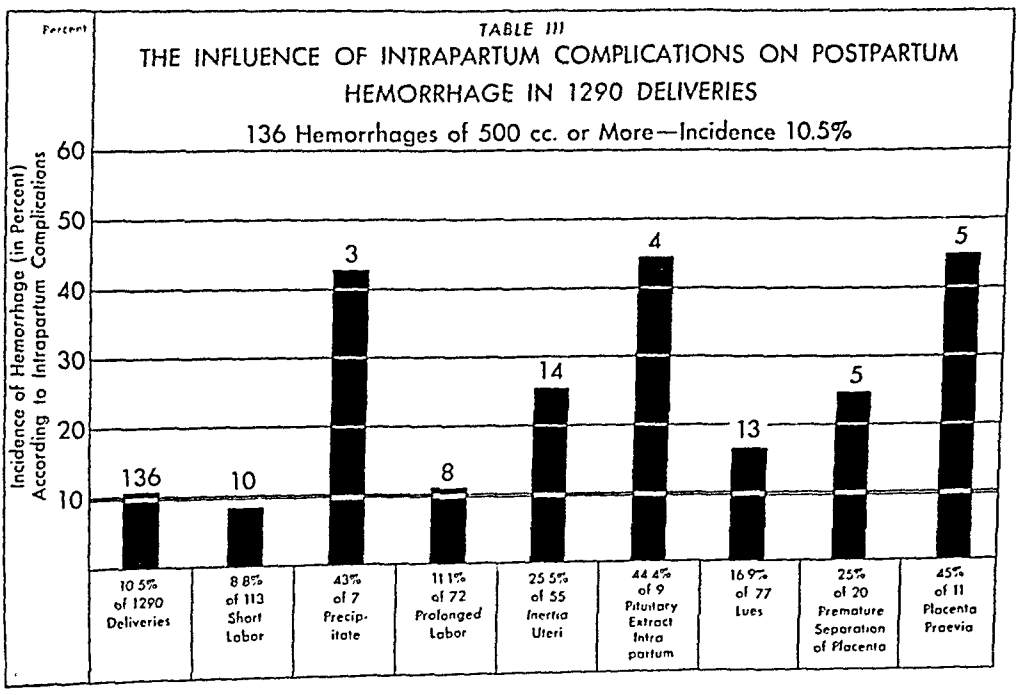
Sulfanilamide and mandelic acid therapy proved effective in *B. coli* infections. Sulfanilamide was useful in hemolytic streptococcal urinary infections while mandelic acid was effective in the presence of *Streptococcus fecalis* which appeared to resist sulfanilamide.

CARL P. HUBER.

possibility of hemorrhage. The anesthesia, when administered inexpertly, or when prolonged, has been found to be a definite factor in increasing blood loss.

2. *Length of Labor.*—(Table III.) Prolonged labor of thirty hours or more, only slightly influenced the chance of excessive bleeding. The short labor of three hours or less diminished the notability, while with the precipitate the expectancy was high.





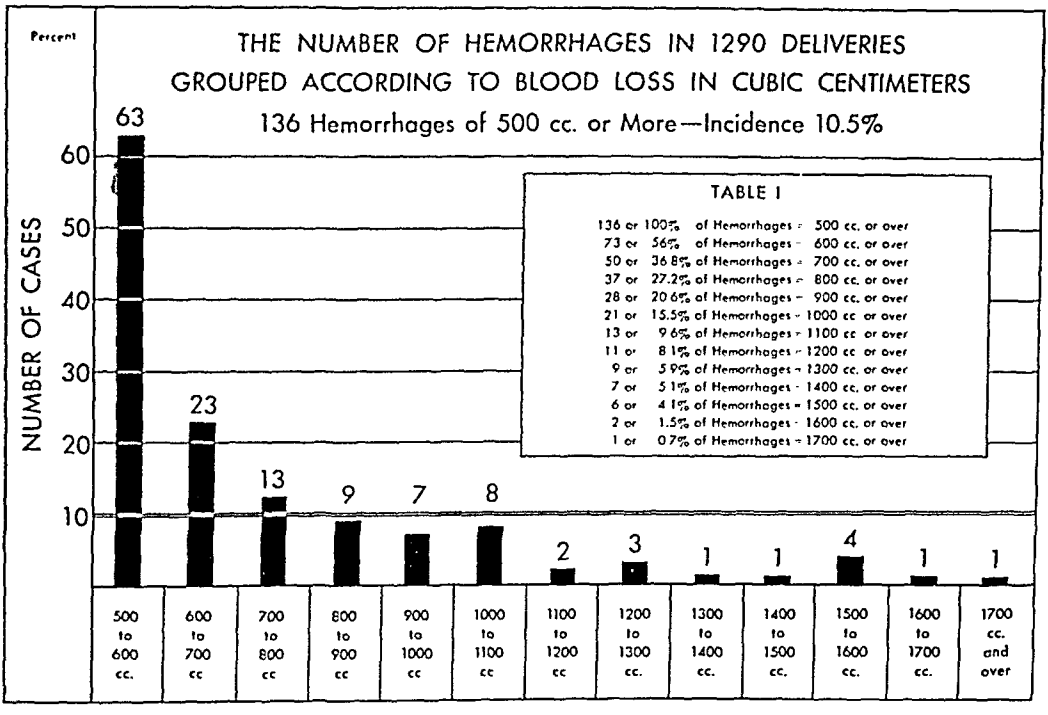
3. *Ante-Partum Uterine Tone.*—In the cases with symptoms of inertia before delivery, post-partum hemorrhage occurred in one out of every four cases. This suggests that the pathologic state is continued into the third stage, and the post-partum related to the ante-partum inertia. When pituitary extract was used intra-partum, there was a startling incidence of hemorrhage later.

the basis of 500; by Calkins with 2 per cent; Pastore 7.1 per cent; Litzenberg 7.1 per cent; Plass 9 per cent; all based on 600 c.c. loss. The relative similarity of these figures based on a large number of cases suggests that when much lower figures are reported the blood loss has not been correctly measured. Table I shows the number of cases in each 100 c.c. group, as well as the number and percentage of hemorrhages above each 100 c.c.

FACTORS INFLUENCING BLOOD LOSS

The hoped for effects from the introduction of a new oxytocic into obstetrics practice must naturally be restricted to the elimination of hemorrhage due to ineffective tone of the post-partum uterus. It is important to examine the causes of post-partum bleeding to determine what fraction may be influenced by a drug acting on the uterine muscle.

Under the following headings one may note certain conditions which merely predispose, but do not actually cause bleeding, such as long



labor, large fetuses, and operative delivery. These may lead to hemorrhage either through their effect on uterine tone or through their production of injuries. The more important classifications are, therefore, the direct causes, such as lacerations and accidents to the placenta, and that of incomplete separation and the retention of a separated placenta during the third stage, as well as retained products post partum, all of these will be largely unaffected by ergotrate, while on the other hand, in post-partum uterine atony, ergotrate may influence the outcome greatly.

1. *Operations.*—(Table II.) The patient with an *operative pelvic delivery* is much more liable to a post-partum hemorrhage. In fact, when breech and low forceps were excluded, the incidence of hemorrhage in this series rose to one case out of every four, which is to be compared with an incidence of only one in twelve of the spontaneous deliveries. In the low forceps cases the incidence was about one in eight. In general, the more difficult the operative procedure, the greater was the

conducive to materially increased blood loss. The detection of the change in shape of the body of the uterus from that of discoid to globular, offers a prompt means of diagnosing complete placental separation. Often the separated placenta fails to drop at once to the lower segment, thereby obscuring the classical picture of placental separation. Too often a detached placenta is allowed to be retained, while the operator completes a plastic pelvic repair.

10. *The Expulsion of the Placenta.*—The proper expression or the Credé method of expulsion requires manipulative procedures that will tend to minimize the blood loss at this time, and is accomplished by obtaining a good uterine contraction, a correct uterine axis, avoiding trauma, and by raising the lower segment out of the pelvis. A complete placenta and membranes should be obtained, and examined for intactness. Manual removal of the partially separated placenta is a surgical procedure that should be instituted in excessive bleedings before the hemorrhage has reached an amount sufficient to present acute symptoms. It is often demanded in cases of placenta previa.

11. *The atony of the post-partum uterus* may thus often be due to errors of commission or omission, but also undoubtedly to intrinsic defects in anatomy or function of the uterine muscle. An empty uterine cavity maintained from the time of the placental delivery will remove an important factor of imperfect uterine functioning. Although possibly of value in some other conditions, notably that of incomplete separation of the placenta post partum, it is particularly in post-partum uterine inertia that we turn for help to the oxytocics.

CLINICAL STUDY OF VALUE OF ERGOTRATE

The isolation in 1934 and 1935 of a new active principle of ergot, variously termed ergometrine, ergostetrine, ergobasin, ergotocin, but chemically identical (Dudley, Thompson, Stoll, Kharasch), has led to several clinical studies, notably those of Adair and Davis, and of Moir.

In 1932 Moir proved that the efficient oxytocic action of ergot was due not to the alkaloids ergotoxine or ergotamine. He used ergot freed of these alkaloids and obtained a superior oxytocic action. It was in 1934 and 1935 that he isolated this previously undetermined substance, which he named ergometrine. All of the above named investigators as well as G. L. Brown and Sir Henry Dale are agreed that its action in the recommended therapeutic doses of 0.2 to 0.5 mg., is entirely limited to that of stimulation of the motility of the parturient and puerperal uterus through the sympathetic system, and for any further pharmacologic action the dose would need to be increased 50 times these amounts.

The special purpose of the study of these 1,290 cases was to compare the clinical value of pituitary extract, ergotamine, and ergotrate (the council accepted, ergonovine, the active principle ergotocine).

A. *The Administration of Ergotrate With the Delivery of the Anterior Shoulder.*—The first phase of this study involved the use of 1 c.c. of ergotrate (0.2 mg. or $\frac{1}{320}$ gr.) intravenously with the delivery of the anterior shoulder in vertex presentations. The cases used for control received pituitary extract 0.5 c.c. intramuscularly, after the delivery of the child and ergotamine tartrate 1 c.c. after the delivery of the placenta. Three hundred and thirty-two cases were studied, 154 with ergotrate, and 178 with the latter method.

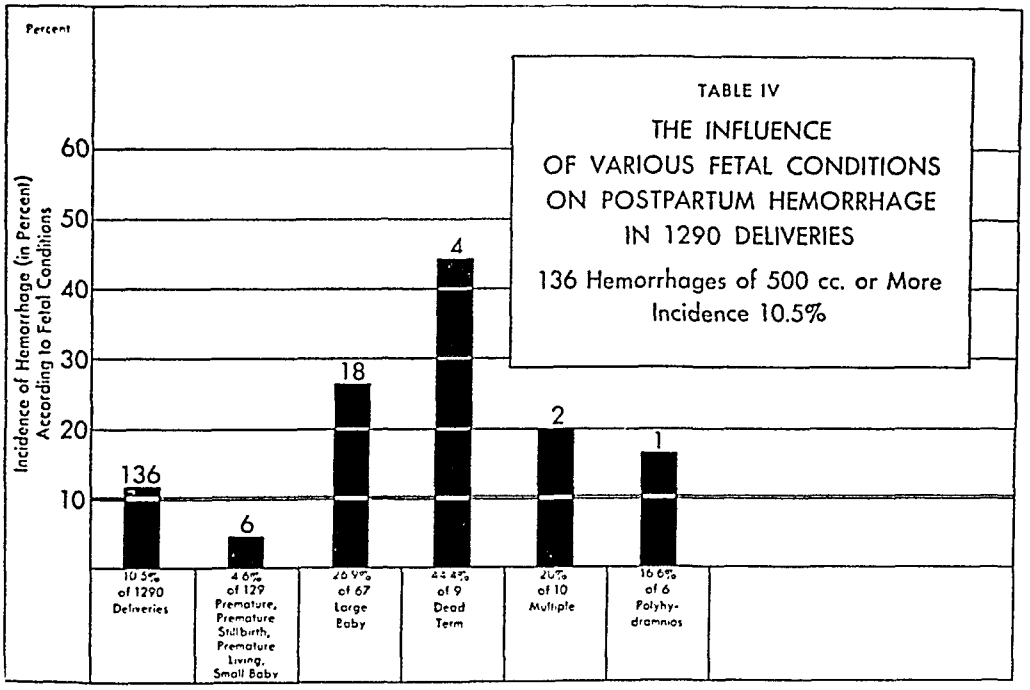
It was found that in the ergotrate series, 86 cases or 55.8 per cent had a blood loss of *less* than 100 c.c., while with pituitary extract and ergotamine tartrate only 46 cases or 28.8 per cent bled less than 100 c.c. On the other hand no hemorrhages of over 900 c.c. were sustained with ergotrate, while 9 occurred without this drug. Six failures with ergo-

4. *The size of the fetus* so frequently having a direct relationship to the size of the placenta, furnishes us with an interesting contrast. With the small baby of five pounds or less, and the premature, the risk of post-partum hemorrhage was found to be less than one in twenty-one, while with the large baby of nine pounds or more, the chances were more than one in four of excessive bleeding occurring. Those term fetuses resulting in stillbirths from a difficult labor were accompanied with a maternal hemorrhage in almost 50 per cent of the cases. Multiple pregnancy and polyhydramnios also increase hemorrhage (Table IV).

5. *Syphilis.*—The occurrence of hemorrhage in one out of six women with positive Wassermann reactions is striking enough to raise the question of the uterine pathology that causes the increased bleeding in this group. It is interesting to note also that 46.1 per cent of this group showed a puerperal infection.

6. *Parity,* per se, was without influence on the incidence of excessive bleedings.

7. *Accidents to the Placenta.*—Premature separation of the placenta with its one in four, and placenta previa with its incidence of almost one in two, were the most consistent causes of continued blood loss after the delivery.



8. *Lacerations.*—Excessive bleeding was the result of tears in 19 cases or in 13.9 per cent of the hemorrhage cases. This is a needlessly high figure since the excessive bleedings from this source are definitely in the preventable group. It would be a conservative rule to inspect cervices at once in the presence of any bleeding in those cases known or suspected to have had a rim of cervix when the delivery occurred, after labors attended with rapid and forceful progress and in cases having had manipulative procedures, as well as in multiparas with cervices known to have extensive cicatricial tissue. Yet it must not be forgotten that even episiotomies increase the blood loss. In four cases of this series the episiotomy was the principal source.

9. *The Separation of the Placenta.*—A partially detached placenta is always hazardous even after the delivery of the baby. To encourage a uterus by manipulation to contract imperfectly before retraction has taken place is to invite this accident, and in our series this abuse has tended to increase the amount and the incidence of hemorrhage. Likewise the failure to recognize and counteract a uterus whose tone is inefficient, or one which is accumulating blood within its cavity, leads to bleedings that are liable to be markedly excessive. On the other hand it must be realized that the placenta often separates completely with the first contraction or with the early contractions. Failure to recognize this occurrence, and promptly to express the foreign body represented by the detached placenta and membranes are

mind of anyone who has used it of its effectiveness in enhancing post-partum uterine tone. The constancy of the maintenance of uterine tone and of its effective contracture obtained throughout a period of two to three hours in the immediate post-partum uterus, affords a security against normal placental site bleedings.

C. *The Administration of Ergotrate After Hemorrhage Is in Progress.*—Although ergotrate finds perhaps its chief use in the prophylaxis of hemorrhage from post-partum uterine atony, it also has a field of usefulness in the treatment of existent hemorrhage. Ergotrate was successfully employed to stop excessive bleeding in 56 of 62 cases in which this use was attempted and pituitrin and ergotamine had failed. In three of the six failures the causes of the hemorrhage suggested local damage to uterine muscle making it unresponsive to any stimulation. Failures were again ascribable to conditions over which ergotrate would not be expected to have any influence.

D. *Ergotrate in Cesarean Section.*—Although no cases are to be here reported, ergotrate has been used in a number of cases of cesarean section on the Bellevue Service during the last two years. There is often a definite place for the administration after the delivery of the child. When it is given, the uterus above the lower segment becomes nearly bloodless, thick, and contracted. At the incised edge, the visceral peritoneum shows as a clearly defined layer. The placenta is freed from its attachment within two minutes, without bleeding from the placental site, provided the implantation is completely in the upper uterine segment. It thus affords nearly ideal conditions for a surgical closure, and, if the placental site is normally situated, the possibility of hemorrhage can be largely eliminated.

E. *Prevention of Hemorrhage as a Prophylaxis Against Infection.*—Excessive blood loss in delivery is not only a direct cause of maternal mortality, but it predisposes to later complications, notably sepsis. This was evident in a study of the present series. The total morbidity, in the 1,290 patients calculated on a standard requiring a rise to 100° on any two days after the first twenty-four hours, was 18 per cent. The morbidity among the 1,154 patients without hemorrhage was 15.1 per cent, but among the 136 patients with hemorrhage, there was the startling figure of 41.9 per cent.

A lowering of this figure may perhaps be accomplished by the more liberal use of transfusions, in the early hours of the post-partum period, to an amount closely commensurate with the loss sustained, as well as by the use of ergotrate to maintain uterine tone in the first three post-partum days. It is now in routine use on the Bellevue Service, 0.2 mg. tablets being given three times a day for the first seventy-two hours.

LIMITATIONS AND COMPLICATIONS OF ERGOTRATE THERAPY TO CONTROL POST-PARTUM BLEEDING

The action of ergotrate is, of course, exclusively upon the uterine smooth muscle. No effect may be expected when the bleeding is from any other site or when gross anatomic damage has been done to the uterine musculature. Failures have been noted by us in cases of placenta

trate were noted. Three of these were due to lacerations, one to placenta previa, another occurred in a premature separation of the placenta.

Ergotrate injected intravenously acts within a minute to produce a series of contractions of the uterus which lead to a more or less tetanic state without intervals of relaxation. The placenta completely separates at once. The tone is maintained, with the surface area considerably reduced, the fundus and body of the uterus do not materially rise in the abdominal cavity. In a few cases an examining hand was placed in the uterus at the time the injection was given, and it was noted that the placenta separated, completely and with practically no blood loss, with the first contraction or about forty-five seconds after the administration of the drug. While in contrast without this drug, placental separation failed to occur within any set time, and with a varying number of contractions.

This rapid and extremely efficient reaction is not without its disadvantages, for in four cases of this group manual removal of the placenta was required due to its retention above a constriction ring in the lower uterine segment. If the ergotrate is to be given at this time as soon as the baby is delivered, it is apparently imperative to express the separated placenta promptly in order to avoid this complication. Since such perfect timing of the expression is not always possible from a practical standpoint, it was decided to try the effect of ergotrate when administered somewhat later.

B. *The Administration of Ergotrate After the Delivery of the Placenta.*—In the second part of the study one group of patients received 0.5 c.c. of pituitary extract intramuscularly after the delivery of the baby and 0.2 mg. or $\frac{1}{320}$ gr. of ergotrate (1 c.c.) intravenously after the placenta, while a control group was given pituitary extract as before, but 1 c.c. of ergotamine instead of the ergotrate, intramuscularly after the placenta. A total of 588 patients received ergotrate after the delivery of the placenta, while 548 belonged to the control group.

In this second series there were 130 patients with a blood loss of over 500 c.c., 42 or 7.1 per cent in the patients treated by ergotrate, 88 or 16.1 per cent in the patients receiving only pituitrin and ergotamine. The contrast becomes more striking when the hemorrhages in the third stage, that is to say before the administration of either ergotrate or ergotamine, are excluded; for if one considers only the late hemorrhages there were only nine after ergotrate or 1.5 per cent of the ergotrate series, but 62 after ergotamine or 11.3 per cent of the control cases.

Failures were again noted in six cases. Two of these were associated with accidents to the placenta, one and possibly others to injury.

There is, of course, a marked variation in the action of the uterine muscle after delivery even without treatment, and the normal variation is carried over into a varied response to the oxytocics. In a clinical classification of the post-partum uterine action the contraction was noted as "good" in only 28.4 per cent of the non-ergotrate group, but in the ergotrate group 89.2 per cent were noted as good. This is, of course, a rather vague classification, but the extreme hardness of the uterus after ergotrate has been given is too characteristic to leave any doubt in the

uterus, contribute to the problem of hemorrhage after the third stage. The predisposing factors which influence excessive bleedings, showed fairly constant ratios in agreement with those analyzed in the tables of the first series. On the other hand the third stage hemorrhages are still high, namely an incidence of 3.3 per cent, and must be dealt with by proper procedures of management, as previously outlined in this paper. Lacerations in the generative tract including rupture of the uterus have taken a heavy toll, and in our series have been the cause of two maternal deaths.

The incidence of post-partum hemorrhage has been reduced 50 per cent in this second year of our study, principally as the result of the negligible occurrence of uterine atony.

CONCLUSIONS

1. Accurate collection and measurements of all blood loss not only during the third stage but for the necessary period of time thereafter, should be established on all obstetric services.

2. Certain factors preceding the third stage influence the blood loss after the delivery.

3. Hemorrhages from lacerations in the parturient canal are often undiagnosed. The incidence and the amounts lost may be high.

4. Greater consideration should be given to the conduct and management of the third stage.

5. Post-partum hemorrhage from the normally situated placental site due to imperfect contraction of the uterus is the chief theoretical indication for an oxytocic. Hemorrhages of this origin are responsible for about 70 per cent of the cases of excessive blood loss incidental to delivery.

6. In a series of 588 patients treated by the administration of ergotrate after the delivery of the placenta, the incidence of a blood loss of 500 c.c. or over was 7.1 per cent as compared with an incidence of 16.1 per cent in 548 cases in which ergotamine tartrate was given instead.

7. When only the blood loss after the third stage is considered, the incidence was 1.5 per cent in the ergotrate series and 11.3 per cent in the control series.

8. Clinical observation indicates that a profound tetanic contraction of the uterus with immediate separation of the placenta if it is still within the uterus occurs within forty-five seconds of the intravenous administration of ergotrate.

9. The use of the drug in 2,500 cases has been accompanied by no systemic reactions. The only complication that has been observed is the occasional retention of the placenta within a tightly contracted uterus when the drug is given at the beginning of the third stage.

10. Ergotrate is superior to other oxytocics in the speed, completeness, and duration of its action and has a definite place in the prophylaxis and control of hemorrhage from the normally situated placental site.

previa with the blood coming from the relatively unresponsive lower uterine segment and in three cases of premature separation of the placenta. In two of the latter, hysterectomy was required to control bleeding, and in each, hemorrhages were found to be present throughout the musculature. Failures were also recorded in cases of placenta partially implanted in the lower uterine segment and in cases of retention of the placenta or membranes. In another unsuccessful case in which hemorrhage had also occurred after two previous deliveries, one may suppose some special endometrial lesion predisposing to bleeding. With these and perhaps a few other exceptions, hemorrhage from the placental site should not occur when ergotrate has been given.

No systemic reaction ascribable to ergotrate was noted in any patient. From our experience with the 742 cases of this series and many more since that time, we feel that the drug can be pronounced as definitely without danger to the patient. Nevertheless the occasional retention of the placenta when the drug is administered at the time of delivery of the child, appears to be a sufficient danger to make the withholding of the drug until after the placenta has been delivered advisable.

A further study of blood loss, following this control series, has been continued on all cases excluding cesarean sections, delivered at Bellevue from April, 1937 to April, 1938, 1,445 in all, during which time it has been routine to use ergotrate intravenously immediately after the placental delivery. This report and its results confirms the previous deductions (Table V).

TABLE V. AN ANALYSIS OF ALL CASES OF PATIENTS WITH POST-PARTUM HEMORRHAGE IN THE SECOND YEAR OF THIS STUDY

1,445 Consecutive Deliveries from April, 1937, to April, 1938, in Which Ergotrate, 0.2 mg. Intravenously, Was Administered After the Placental Delivery, as a Routine Procedure

			INCIDENCE
80 Patients with hemorrhage of 500 c.c.			5.37%
52 Patients with hemorrhage of 600 c.c. or over			3.5 %
CAUSES	CASES	PERCENTAGE	INCIDENCE
Uterine atony	13	16.2	0.89%
Lacerations			
Uterus, cervix, vaginal, perineal	14	17.5	
Third stage			
Incomplete separation and with delivery of placenta	48	60.0	3.3 %
Placenta previa	5	6.2	

NOTE: Of the thirteen cases of uterine atony, 3 patients had retained cotyledons and 2 had ablatio placentas, one of which necessitated a hysterectomy. This leaves 9 patients in whom ergotrate was ineffective in producing good tonicity.

DISCUSSION

It may be concluded from this second series of cases on the Bellevue Hospital Service, that uterine atony as a cause of post-partum hemorrhage has been reduced to a minimal degree, namely to an incidence of 0.89 per cent by the use of ergotrate intravenously. Also that placenta previa, low implantations of the placenta, and premature separations of the placenta, as well as the failure to secure an empty

We have approached the problem by a complete study of the female first, adhering to the following routine: history, general physical examination, pelvic examination, complete blood count, urinalysis, Wassermann, basal metabolic rate, premenstrual blood hormone studies for estrogenic substance[4] and for gonadotropic substance,[5] premenstrual endometrial biopsy,[6-9] tubal insufflation,[10] postcoital vaginal pool examination.[11] Other procedures as x-ray, blood chemistry, etc., were resorted to when they were indicated.

CLASSIFICATION OF ETIOLOGIC FACTORS

A classification of the etiologic factors in sterility must, of necessity, be an arbitrary one since the specific factors are numerous, may occur singly or in many combinations, and assume a varying degree of importance in different cases. We have grouped these factors in large groups as follows, recognizing that with this grouping, as with any other, there is bound to be overlapping:

I. Factors in the Female
 1. Constitutional abnormalities
 2. Organic pelvic pathology
 3. Closed tubes
 4. Endocrine abnormalities

II. Factors in the Male
 1. Sexual incompetency

It is quite probable that constitutional factors do not carry the significance in sterility which is sometimes attributed to them, but they can not be ignored. Any abnormal finding on pelvic examination is important. Closed tubes are listed as a specific entity due to their frequency and importance as a cause of sterility. We have especially stressed endocrinologic investigations and have classified the evidences of glandular dysfunction as general endocrine stigmas, abnormal blood hormone levels, and abnormal endometrial patterns.

ENDOCRINE STIGMAS

General endocrine stigmas are merely findings suggestive of endocrine imbalance and are not considered to be primary causes of sterility. They include abnormalities of growth and development, menstrual irregularities, and disturbances of body metabolism. Basal metabolic rates not within the limits of the normal may be considered as a general factor since such findings occur in many types of endocrinopathies other than primary disturbances of thyroid.

ABNORMAL BLOOD HORMONE LEVELS

The premenstrual hormone tests were interpreted as follows: A positive estrogenic and a negative gonadotropic reaction is the normal finding. Complete absence of both the estrogenic and gonadotropic substance denotes primary pituitary failure. Absence of the gonadotropic substance with deficient estrogenic substance or in some instances, exces-

11. Puerperal infection and other morbid processes are materially influenced and dependent on the presence of large blood losses. The cell volume should be restored promptly to a normal amount by the use of transfusions in sufficient amounts.

We are indebted to Dr. John B. Pastore for the special construction of a portable Pastore blood measuring apparatus which enabled us to accurately measure blood loss.

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ETIOLOGIC FACTORS IN STERILITY*

Report of Study of One Hundred and Fifty Cases

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THE advent of new methods in the study of sterility and the development of new concepts of the physiology of reproduction have given a fresh impetus to the investigation of the problem of the sterile marriage. To emphasize the necessity of a complete and detailed survey of the sterile couple, it seemed that a review of the etiologic factors in a series of cases and the relation of the type and number of these factors to the results obtained after treatment might be of value.

The cases herewith reported are derived entirely from our private practice. They represent the patients who applied to us during the past four years with the primary complaint of sterility. There were 169 such cases. Ten of these did not elect to undergo the study as outlined to them, 9 patients were advised to try for a pregnancy for a longer period of time. We, therefore, had 150 cases of sterility which we were able to study completely.

METHOD OF STUDY

The methods of determining the etiologic factors in sterility have been elaborated by other investigators,[1-3] and we need not go into detail here. Suffice it to say that each investigator must establish a definite routine suitable to his own group of cases and follow it carefully in every case.

*Read at a meeting of the Washington Gynecological Society, March 26, 1938.

castration following hydatidiform mole. There were 13 cases with closed tubes which could not be opened upon repeated inflations and in which operation was not deemed advisable or was refused by the patient. These cases with closed tubes were further complicated by the occurrence of male incompetence in 7 cases and female endocrine factors in 7 cases. Pelvic inflammatory disease with closed tubes accounted for 5 cases. There were only 2 cases in which male incompetency was the only cause.

Causes of Relative Sterility.—Relative sterility, which constituted 80 per cent of the cases studied, was found to be due in most instances to multiple factors. It is in this type of sterility that the milder degrees of abnormalities are most significant. The incidences of these factors were as shown in Table I.

TABLE I. TYPES OF ETIOLOGIC FACTORS PRESENT IN 150 CASES OF STERILITY

Absolute Sterility, 30 cases	
Primary Sterility, 18 cases	
Constitutional abnormalities	9
Organic pelvic pathology	7
Closed tubes	13
Endocrine abnormalities	8
Male sexual incompetency	9
Secondary Sterility, 12 cases	
Constitutional abnormalities	4
Organic pelvic pathology	10
Closed tubes	7
Endocrine abnormalities	3
Male sexual incompetency	4
Relative Sterility, 120 cases	
Primary Sterility, 86 cases	
Constitutional abnormalities	70
Organic pelvic pathology	35
Closed tubes	38
Endocrine abnormalities	52
Male sexual incompetency	19
Secondary Sterility, 34 cases	
Constitutional abnormalities	29
Organic pelvic pathology	17
Closed tubes	16
Endocrine abnormalities	20
Male sexual incompetency	8

Constitutional Factors.—In the relative sterilities, constitutional factors occurred 99 times with the following distribution of cases: overweight 23, underweight 15, focal infection 25, anemia 30, arrested tuberculosis 1, chronic kidney disease 2, chronic heart disease 1, goiter 2.

Pelvic Pathology.—As might be expected, the type of pelvic pathology encountered in the relative sterile group was less severe than in the absolutely sterile group. In the 52 instances of this type of factor, the conditions encountered are listed in the first columns of Table II.

Closed Tubes.—Since this condition was present in 54, or 45 per cent, of the cases of relative sterility, a search was made for significant facts in the history and examination of each which might account for the condition. In 15 cases, there was nothing found to account for the closed tubes. In the remaining cases, there were from one to four facts noted in each as possible causative factors. They were: fibroid uterus 1, pelvic inflammatory disease 16, endocervicitis 5, retroversion 7, infantile uterus 3. There was a history of gonorrhea in 10 cases and of abortion in 17 cases. Previous operation for appendicitis had been performed in 18 cases. It appears, therefore, that there is no single etiologic factor in closed tubes but that they may result from any type of acute or chronic pelvic inflammation.

sive amounts of the estrogenic substance denotes partial pituitary failure. Deficient estrogenic substance with excessive amount of the gonadotropic substance indicates primary ovarian failure. The greatest value of the hormone tests is the differentiation thus obtained between primary and secondary ovarian failure. The degree of ovarian failure is best obtained by study of the endometrium.

ABNORMAL ENDOMETRIAL PATTERNS

In the normal premenstrual endometrium there is a well-differentiated secretory reaction. In our study of sterility, we have encountered several types of secretory endometria which we consider distinctly abnormal. In such cases, the glands may be fewer in number, the secretory reaction irregularly and poorly developed or there may be a mixed reaction in which some of the glands show a secretory differentiation while others are still in the follicular phase. In still another type the secretory reaction may be superimposed on an abnormal follicular reaction or associated with cystic changes in the glands. These findings, we believe, are especially important in sterility since they indicate a disturbance in the balance of the two ovarian hormones during the luteal phase of the ovarian cycle.

A more profound type of ovarian failure is evidenced by the presence of the follicular phase of the endometrium premenstrually, with or without cystic changes. Such an endometrium indicates the absence of corpus luteum function and usually anovulatory menstruation. We have found[12] that there is no distinct correlation between the type of endometrium and the character of the menstrual flow. Since this is true, these factors in sterility, abnormal hormonal balance and failure of ovulation, would be entirely missed if the endometrium is not studied.

MALE INCOMPETENCY

The diagnosis of sexual incompetency in the male was based on postcoital examination of the vaginal pool and the condom examination when necessary. Only those findings which were corroborated by the further study of a urologist are reported.

RESULTS OF STUDY

Incidence of Etiologic Factors.—The incidence of the types of sterility and the types of etiologic factors in sterility are summarized in Table I. There was an incidence of 378 for all the types of factors in the 150 cases or an average of two and one-half types of factors in each couple. Since each type may represent several abnormalities further analysis revealed an average of five and one-fifth specific factors for each couple.

Causes of Absolute Sterility.—The diagnosis of absolute sterility was made in most cases upon the presence of definite organic pathology. In no case were constitutional or endocrine factors alone the cause of the sterility although they occurred as contributing factors. There was usually one outstanding finding which could be designated as the primary cause of the sterility and which could not be remedied to restore the fertility of the patient. The specific causes were as follows: The tubes had been previously removed in 4 cases. A large fibroid uterus was present in 4 cases, in 2 of which the tubes were closed also. There was 1 case of bilateral chocolate cysts of the ovaries and one of sclerotic ovaries due to radium

the city or those who did not elect to undergo the treatment outlined. Twelve patients did not follow the treatment for the prescribed time. Seventy-eight patients with relative sterility were treated. There have been 41 pregnancies, 35 of which were normal, 5 miscarriages and 1 was ectopic. There were no instances of fetal abnormalities. Thirteen cases were considered failures, and 24 patients are still under treatment.

Single-Cause Sterility.—Sterility due to a single cause is rare. Sterility due to a single type of cause occurred in only 28 cases, or 18 per cent, of the 150 cases studied. When these cases were analyzed as to specific abnormalities, the number of sterilities due to a single fault was found to be 8. Of the 28 cases, pelvic pathology accounted for 5, closed tubes 7, endocrine factors 14, and male incompetency 2. Constitutional factors did not occur alone as the cause of sterility. The total number is too small for the percentage to be significant. The most suggestive finding is that the endocrine factors constituted about one-half of the entire group and was twice as frequent as closed tubes the second most common cause. In all of the cases of endocrine dysfunction, the findings were identical, i.e., infantile uterus, follicular premenstrual endometrium and low basal metabolic rate. It would seem, therefore, for endocrine dysfunction alone to produce sterility, the glandular failure must be fairly severe.

Of the 28 patients having a single type of etiologic factor 9 received incomplete or no treatment. In the 19 patients treated there have been 12 pregnancies. The specific causative factors in the patients who became pregnant were: endocervicitis 1, pelvic congestion 1, closed tubes 4, and endocrine factors 6. The percentage of success, which is 63 per cent, is considerably higher than that of the whole group of treated patients where pregnancy occurred in 52 per cent of the patients.

Age of the Patient and Duration of the Sterility.—The age of a sterility patient when she applies for treatment is usually considered to be a significant factor. However, in the group studied, there was little variation among the different types of sterility (Table III), and all represented patients during the active reproductive stage of life. Analysis of the completely treated cases reveals that in the group in which pregnancy occurred, the average age was slightly lower and the duration of the sterility shorter. The range of the ages and duration of sterility in the successes and failures show that this rule does not always hold true. Age is important, therefore, in evaluating the significance of other factors.

Secondary Sterility.—In reviewing the previous histories of the 46 cases of secondary sterility which are summarized in Table IV, it becomes evident that the background of these patients indicates that they represent a group whose fertility is lowered irrespective of the factors operative at the time of the study. The num-

TABLE III. AGE OF PATIENT AND DURATION OF STERILITY

	NO. OF PATIENTS	AGE RANGE	AVERAGE AGE	YEARS OF STERILITY	AVERAGE DURATION OF STERILITY
Absolute Sterility:					
Primary	18	18-36	30	1-7	5.5
Secondary	12	22-37	28	2-8	4.0
Relative Sterility:					
Primary	86	19-39	27	1-18	4.0
Secondary	34	25-41	32	1-11	4.5
Patients Pregnant:					
Primary	26	20-40	27	1-18	4.0
Secondary	15	25-41	32	1-11	3.5
Failures:					
Primary	9	25-40	33	2-16	8.0
Secondary	4	25-28	31	1-7	4.0

TABLE II. PELVIC PATHOLOGY AS A FACTOR IN RELATIVE STERILITY

	CASES STUDIED	CASES TREATED	
		CASES PREGNANT	FAILURES
No. of cases	120	41	13
Instance of pathology	52 or 43%	19 or 46%	7 or 53%
Inflammation	17 33	4 22	5 62
Congestion	8 15	6 33	0 0
Endocervicitis	15 29	4 22	0 0
Retroversion	4 8	3 15	1 12
Fibroid	1 2	0 0	1 12
Infantile uterus	7 13	2 10	2 24

Endocrine Abnormalities.—According to our definition of endocrine factors, they were present in 72 cases. These cases were further grouped on the basis of the endometrial findings because we consider this the most accurate method of determining the state of ovarian function. Since our series dates back four years, biopsy findings were absent in 25 cases. The remaining 47 cases with endocrine factors fell into the following groups: normal premenstrual secretory endometrium 18, faulty secretory endometrium 12, follicular premenstrual endometrium 17.

In the group having a secretory endometrium the only significant findings were low basal metabolic rate in 13 cases, infantile uterus in three cases, and, one case each of oligomenorrhea and polymenorrhea. There was no instance of hormone imbalance in the blood. These cases, therefore, had normal ovarian function and the endocrine factors were of little significance.

In the group having a faulty secretory endometrium there was an increase in the incidence of other endocrine factors. Estrogenic deficiency was present in five cases. Oligomenorrhea occurred in 6 cases, polymenorrhea in 1 case, and the basal metabolic rate was below normal in 4 cases. All of these cases, therefore, represent partial secondary ovarian failure.

In the group having a follicular type of endometrium premenstrually, there was a marked increase in the associated endocrine factors. For the whole group, there were 60 specific positive findings of an endocrine nature, no case having less than two factors, 1 case had five, 8 cases had four, 7 cases had three, and 1 case had two. The hormone level was abnormal in all 17 cases, 10 having a low level of estrogenic substance and 2 having an excess of the gonadotrophic substance. Oligomenorrhea occurred in 10 cases and polymenorrhea in 2 cases. The basal metabolic rate was low in 11 cases. In all 17 cases, there were marked ovarian deficiencies, 2 of which were primary and 15 secondary.

The 25 cases in which no biopsy was done represent a heterogenous group. The blood hormone level was abnormal in 11 cases, there being 2 cases of excessive estrogenic substance, 6 of deficiency of the estrogenic substance, and 3 cases of excessive gonadotrophic substance. The basal metabolic rate was low in 12 cases. Oligomenorrhea was present in 12 cases and polymenorrhea in 1 case.

Male Incompetence.—In the cases of relative sterility male incompetence was a factor in 27 cases.

RELATION OF ETIOLOGIC FACTORS TO THE RESULTS OF TREATMENT

There is no specific routine of treatment for sterility. The one aim is to correct as many faults as possible. For the majority of the factors outlined, the methods of treatment have been well established. Our only variation which might be mentioned here is the use of x-ray to the pituitary and ovaries in the cases with disturbed function of these glands, which method we have used extensively in many types of functional disorders of the female.[13]

Of the 120 cases of relative sterility, 30 received no treatment by us. They represent patients sent for diagnostic study alone, patients who left

gree of ovarian failure and prognosis for therapy is evidenced by the change in ratio of success and failure with the change in the endometrium from a secretory to a follicular type of reaction as shown in Table VI. Pseudomenstruation and possibly anovulatory menstruation, occurred in 17 patients of the group with endocrine factors in which a biopsy was done, in 7 of those who became pregnant and

TABLE VI. ENDOCRINE FACTORS IN RELATIVE STERILITY

	CASES STUDIED	PATIENTS TREATED PREGNANT	FAILURES
Number of patients having endocrine factors	72	23	13
Secretory endometrium	18	11	0
Abnormal secretory endometrium	12	7	2
Follicular endometrium	17	7	5
Excessive blood estrogenic substance	7	1	0
Deficient blood estrogenic and gonadotropic substance	21	11	7
Excessive blood gonadotropic substance	5	11	3
Low basal metabolic rate	40	12	5
Menstrual irregularities	34	12	7

in five of the failures. Since biopsy was not performed in some of the cases it is entirely possible that this figure should be higher, but it at least represents a minimum figure for the incidence of this condition. The blood hormone studies indicated that there were 33 cases of definite ovarian failure, 5 of which were primary in the ovary and 28 of which were secondary to other deficiencies. Of the 13 patients who became pregnant, 12 were of the secondary type and only 1 was due to the primary ovarian deficiency, while in the cases of failure there were 3 cases of primary ovarian deficiency and 7 cases of a secondary type. It would seem, therefore, that the occurrence of primary ovarian failure renders the prognosis more grave. Menstrual irregularities are merely indicative of ovarian dysfunction but are not diagnostic of the type or degree of ovarian failure. A low basal metabolic rate did not occur as the only specific endocrine cause of sterility though it was a contributing cause in more than half of the cases.

SUMMARY

In this study, the findings in 150 cases of sterility have been reviewed. It was found that in every sterile couple there was a multiplicity of factors operative. Absolute sterility was always due primarily to a specific organic pelvic pathologic condition. Relative sterility was usually due to many less serious factors. The secondary sterilities, as judged from their past histories, had a lowered fertility irrespective of the factors operative at the time of the examination.

In the relative sterilities, pelvic pathology, closed tubes, endocrine factors and male incompetence were the causes of the sterility, the significance of each being dependent upon the severity of the condition and its association with other factors. Sterility due to a single fault was rare.

Constitutional factors were not found to be the cause of sterility in any case.

Endocrine factors were found to be important in the production of sterility. Blood hormone tests are valuable in determining the etiology of ovarian failure. The endometrial biopsy is the most accurate method of determining the type and degree of ovarian failure.

ber of completely treated patients with secondary sterility is too small for significant analysis, but it seems that their chances of pregnancy are about equal to those of the primary sterility.

TABLE IV. PREVIOUS PREGNANCIES IN THE SECONDARY STERILITIES

	ABSOLUTE STERILITY	RELATIVE STERILITY	PATIENTS TREATED PREGNANT	PATIENTS TREATED FAILURE
Total No. of cases	12	34	14	4
Total pregnancies	15	49	27	8
Normal pregnancies	5	13	5	4
Spontaneous abortions	9	22	9	3
Induced abortions	0	11	12	1
Ectopic pregnancy	1	0	0	0
Prematurity	0	1	0	0
Hydatidiform mole	0	1	0	0
Eclampsia	0	1	1	0

Pelvic Pathology.—The incidence and type of pelvic pathology is summarized in Table II. Pelvic inflammatory disease accounted for the largest percentage of pelvic lesions and was the most frequent factor of those cases in which no pregnancy occurred. Endocervicitis and congestion are factors which may produce sterility but are easily corrected as shown by the fact that their incidence was high in the whole group studied and in those who became pregnant, but they were absent as a causative factor in the group of failures. Retroversion alone seems to be of little significance since pregnancy occurred in three of the four patients in whom it was present, though nothing was done to correct the retroversion. The importance of fibroids depends upon the number, size, and location of the tumors. An infantile uterus is of significance only when the endometrium indicates abnormal ovarian function.

Closed Tubes.—The incidence of closed tubes and the results of inflations are listed in Table V. Of the 54 relative sterilities with closed tubes, 36 were opened by repeated inflations. The result is probably lower than should actually be the case since the total number includes 7 patients in whom the tubes were inflated only once. Of the completely treated cases, there was an incidence of 19 closed tubes of which 16 were opened by inflation. The presence of closed tubes alone does not, therefore, render the prognosis in sterility grave. More important are the associated conditions, especially the presence of pelvic pathology which destroys the motility of the tubes and disturbs the function of the ovaries.

TABLE V. CLOSED TUBES AS A FACTOR IN RELATIVE STERILITY

	CASES STUDIED	PATIENTS TREATED PREGNANT	PATIENTS TREATED FAILURES
No. of Cases	120	41	13
Partially Closed Tubes:			
Number	24	6	2
Opened	18	6	2
Number of inflations	1-9	2-9	3
Average No. of inflations	3	3	3
Completely Closed Tubes:			
Number	34	8	3
Opened	18	8	0
Number of inflations	1-12	1-10	7-12
Average No. of inflations	5	6	9

Endocrine Factors.—The importance of a thorough endocrine survey is demonstrated by the frequency of occurrence of endocrine factors. Such factors were found in 72 of the total cases studied, in 23 of the patients who became pregnant and in 10 of the failures. The value of the endometrial study for diagnosis of de-

During this period there were 15,488 deliveries (Table I), 4,062 being private or semiprivate cases. There were 944 deaths, giving a total mortality of 6.1 per cent. In the private group of 4,062 cases (Table VII) there were 98 deaths, a total mortality of 2.4 per cent. The corrected mortality considered 403 infants, 40 of which were among the private cases, giving a corrected mortality of 2.6 per cent for the entire group and 0.98 per cent for the private cases. Stillbirths accounted for 48 per cent and neonatal deaths for 52 per cent of the group; 35 babies obviously died during delivery.

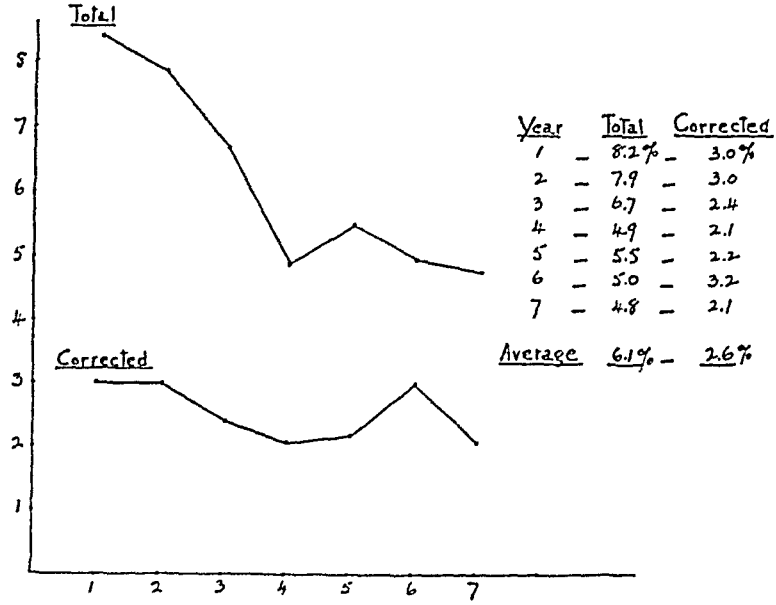


Chart 1.—Total and corrected mortality for seven years.

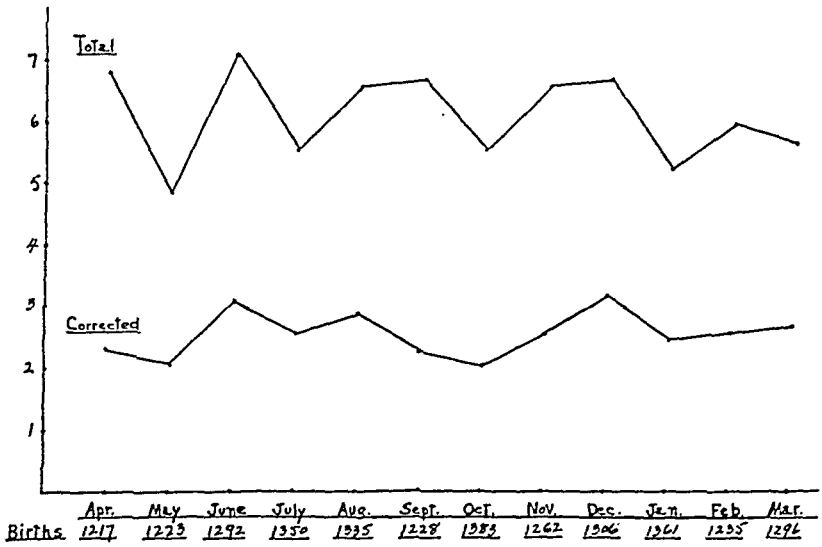


Chart 2.—Seasonal incidence.

A very interesting and satisfactory result of this study has been the steady decline in both total and corrected mortality rates, as shown graphically in Chart 1. The former dropped from 8.2 per cent to 4.8 per cent and the latter from 3 per cent to 2.1 per cent. In Chart 2, the seasonal incidence of deaths in both total and corrected groups is shown. There does not seem to be any correlation between seasonal infections

CONCLUSION

There is no short cut in the management of cases of sterility. Every case must be studied diligently to determine every possible causative factor which may be present and an effort made to correct every defect which is found.

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NEONATAL MORTALITY AT THE PHILADELPHIA LYING-IN HOSPITAL*

A Seven-Year Study

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IN THE past thirty years great strides have been made in the reduction of infant mortality under one year of age, dropping from 166 to 53 per 1,000 live births. During this same period of time little reduction has occurred in neonatal mortality. In fact, it has been shown that the mortality of the first twenty-four hours of life has been increasing. This in all probability is due to prematurity and other related factors. In the series studied in this report, 65.5 per cent of the neonatal deaths occurred in the first twenty-four hours, and 44.7 per cent lived less than six hours.

Ten years ago the staff of the Philadelphia Lying-in Hospital began a more careful analysis of our infant deaths. All infant deaths were discussed at the monthly staff meetings and attempts were made to ascertain the circumstances concerning these deaths, and to fix individual responsibility. Errors in judgment, in technic and in methods were pointed out. The data in this report begin with April, 1930, and continue for seven years, including both private and ward cases. Particular effort was made in analyzing deaths of all babies over 4 pounds who did not have an obvious malformation. Our total mortality includes all babies for whom a birth certificate is required by the laws of the state of Pennsylvania. The age base is twenty weeks or more. Our corrected mortality was secured after babies under 4 pounds and those with obvious malformations not compatible with life were eliminated.

*Read at a meeting of the Obstetrical Society of Philadelphia, March 3, 1938.

per cent. In Chart 3 the seasonal incidence of twin births is shown. We have no explanation as to why there are three times as many births of twins during the month of August as in any other month of the year.

The relation of birth weight to neonatal deaths, as shown in Table II, has been explained on numerous occasions in various reports. In this group studied there were 579 premature babies, for 74 of which the birth weight was not stated; 277 of

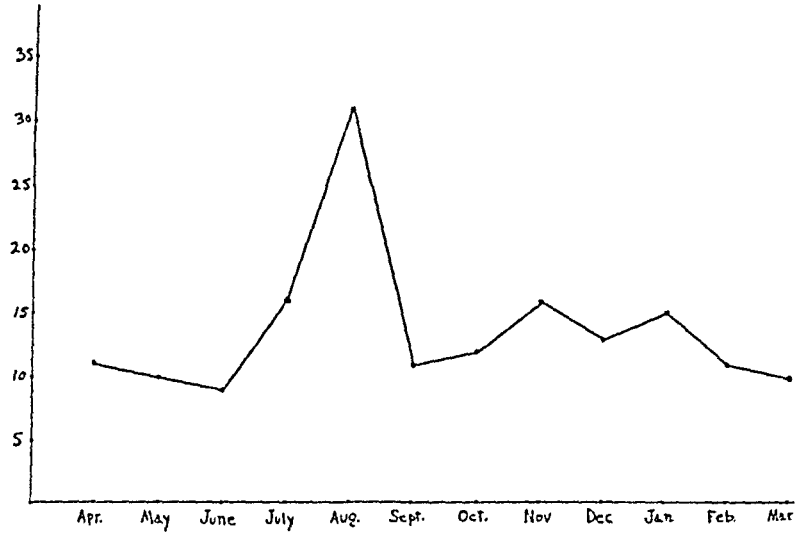


Chart 3.—Seasonal incidence of twin births.

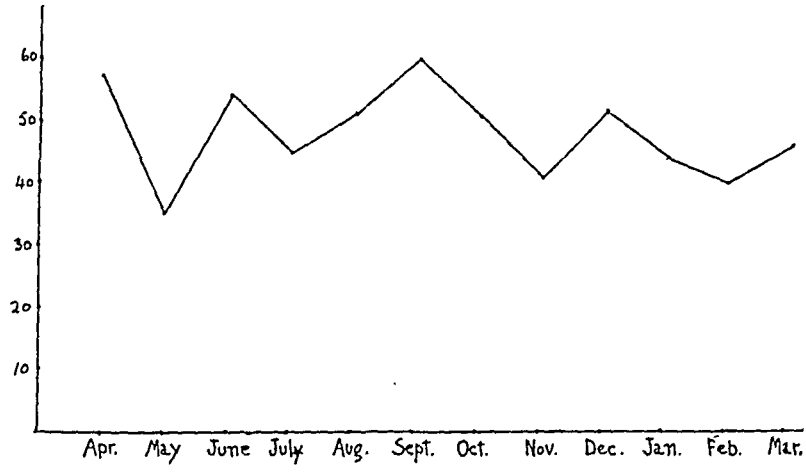


Chart 4.—Seasonal incidence of premature deaths.

these babies weighed less than 3 pounds, and all of them weighed less than 5 pounds. The mortality of prematures varies inversely with the weight, that is, as the weight decreases the mortality increases. There does not seem to be any relation between premature deaths and seasonal incidence of infections. Chart 4 shows graphically the number of premature deaths occurring in the various months of the year. Most of the prematures who die did so in the first twenty-four hours, before infection would have much chance to get started.

The relation of the hours of labor to mortality could be definitely established in 802 of our cases (Table III). In the rest of the group, either because of their being emergencies or too indefinite, the hours of labor could not be determined. It is interesting to note that in 560 of the cases the hours of labor exceeded six hours. In 112 of them it was over twenty-four hours. Because of the difficulty of differentiating between the first and second stages of labor in so many of the cases, this detail was omitted in all.

TABLE I. APRIL, 1930, TO APRIL, 1937

Total deliveries	15,488
Mortality	944— 6.1 per cent
Stillbirths	461—48.0 per cent
Deaths	483—52.0 per cent
Deaths during delivery	35
Corrected mortality	403— 2.6 per cent

and births and deaths. An enthusiastic staff with a sincere desire to improve, and working harmoniously, is perhaps the best explanation to be offered for the reduced mortality. The mature judgment of the older obstetricians and more skilled technic in handling difficult cases, perhaps accounts for the excellent results in the private cases. Closer supervision by the junior obstetric staff over the work of the residents and interns, whereby an experienced obstetrician is in attendance at all times, might be cited as another explanation.

During this period of study there were 461 stillbirths. This constitutes 48 per cent of the total deaths and is at the rate of 30 per 1,000 live births. This compares favorably with the rate for the United States for the years, 1933, 1934 and 1935, when it was, respectively, 38.9, 36.7, and 34.2.

INCIDENTAL FACTORS

A number of incidental factors are of interest in this group studied. There were 56 per cent males and 44 per cent females. This is approximately a ratio of 100 deaths in females to 127 deaths in males. Again this bears out the vulnerability of the male, which is essentially the same in other diseases, especially pneumonia. There were 61 per cent white babies and 39 per cent colored; 42 per cent of the deaths occurred in primiparas and 58 per cent in multiparas; 61 per cent of the deaths were prematures and 39 per cent were full-term children. Autopsies were secured in 594 or 63 per cent of all cases.

MULTIPLE BIRTHS

Twin deliveries during the seven-year period of study represented 2.1 per cent of the total deliveries. The influence of multiple births on neonatal mortality is shown in our records; 336 babies were the result of multiple births; 165 twin deliveries and 2 sets of triplets occurred during the seven-year study period. In 28 sets of twins both of them died; in 11 other instances one of the twins died and 1 set of triplets died. In all there were 70 deaths, or 7.4 per cent of the total deaths were associated with multiple births (Table VI). The mortality in twins is 20.3 per cent, the mortality in triplets is 50 per cent. The total mortality in multiple births is 20.8

TABLE II. BIRTH WEIGHT AND PREMATURE DEATHS

Under 2 pounds	137	505
2 to 3 pounds	140	
3 to 4 pounds	125	
4 to 5 pounds	103	
Birth weight not stated	74	
Total	579—61 per cent	

the very small premature babies. It is this group that is so often spoken of as belonging to the general debility class. This is a very inclusive term and does not help for accuracy. Many believe such a diagnosis can be supported, although our efforts have been to assign a more definite reason for the deaths of these infants, if it is at all possible. It is probably in this group that we see the results of abnormal biochemical relationships and anatomic and physiologic inadequacies in the infant. The problem seems to be to enable the infant to remain longer in the uterus until its physiologic processes are able to function after separation from the mother.

CAUSES OF DEATH

In attempting to outline the causes of death (Table VI) in this group of babies, it was found that there was a great deal of overlapping; that is, two or three conditions could readily exist in the same case, as for example, a syphilitic mother might develop toxemia and give birth to a premature infant. To make a differential classification is not an easy task. Again, it was found in looking over the records of the mothers that certain conditions of health in the mother, other than syphilis and toxemia, might have had decided influence in determining the condition of the child when born. The diseases in the mother that could have had some influence were 8 cases of pneumonia, 15 cases of rheumatic heart disease, 5 cases of diabetes, 2 of tuberculosis, 14 of pyelitis, 18 cases in which an injury or a fall occurred, 3 cases of severe secondary anemia, 8 cases of acute bronchitis, 4 cases of myoma of the uterus, 1 case of severe asthma, and 1 of encephalitis. Again, the causes of death were somewhat influenced by 75 emergency cases. These were women who were not known to the hospital, had had no prenatal care, and either had attempts at delivery at home or perchance the child was born en route to the hospital or was delivered shortly after arrival. Undoubtedly many of these cases were severe and often complicated. So far as possible, however, the cause of death is listed according to the main factor. Again, it seemed important that we should separate the stillbirths from the neonatal deaths, remembering that 48 per cent of our total mortality were stillbirths and 52 per cent were neonatal deaths.

TABLE VI

CAUSE OF DEATH	STILLBIRTHS		NEONATAL DEATHS		TOTAL		350 CASES WITHOUT AUTOPSY	
	CASES	%	CASES	%	CASES	%	CASES	%
Prematurity	121	26.2	157	34.0	278	30.1	113	32.2
Asphyxia	86	18.6	55	11.9	141	15.2	43	12.2
Syphilis	70	15.0	35	7.5	105	11.2	33	9.4
Trauma	46	9.9	66	10.4	112	10.1	17	4.8
Toxemia	53	11.4	25	5.4	78	8.4	33	9.4
Infections	--	---	50	10.8	50	5.2	13	3.7
Malformations	29	6.2	41	8.4	70	7.5	19	5.4
Hemorrhage	3	0.6	26	5.6	29	3.1	4	1.1
Unknown	55	11.9	24	5.0	79	8.4	65	18.5
Other diseases in mother							10	2.8

PREMATURITY

Prematurity undoubtedly is the main factor in causing such a high neonatal mortality, and as was to be expected heads the list as the cause of death in the group studied. In the 579 premature infants it was possible to find a definite cause of death in 301 cases. In the remaining 278 the cause was given as prematurity alone. There were 121 babies or 26.2 per cent of the stillbirths, and 157 or 34 per cent of the neonatal deaths that were thought to be due to this cause. When the 350 cases that did not have autopsy were considered, it was found that 32.2 per cent of this group were stated as due to prematurity. It was not always possible to de-

TABLE III. HOURS OF LABOR

Up to 3 hr.	86	
3 to 6 hr.	156	
6 to 12 hr.	228	
12 to 24 hr.	220	560
Over 24 hr.	112	
Total	802	

The relationship of the types of deliveries and mortality resulting therefrom is shown in Table IV. The lowest mortality rate occurred in forceps when applied to the vertex. Deliveries by this method made up 50.4 per cent of the total, while it only accounted for a mortality rate of 2.3 per cent in that group. The 185 deaths in this type of delivery made up 19.6 per cent of all the deaths. Mid, low, and outlet forceps were the obstetric procedures. There were 5,830 spontaneous vertex deliveries, making up 37.6 per cent of the total deliveries. In this group there were 440 deaths, yielding a mortality of 7.5 per cent, while the 440 deaths accounted for 46.6 per cent of all the deaths. In searching for an explanation as to why the mortality rate in spontaneous vertex is almost three times that of forceps applied to the vertex deliveries, it is noted that there were 251 in the spontaneous group

TABLE IV. TYPES OF DELIVERY

	TOTAL	PER CENT OF TOTAL	DEATHS	MORTALITY PER CENT	PER CENT OF DEATHS
Spont. vertex	5,830	37.6	440	7.5	46.6
Forceps vertex	7,814	50.4	185	2.3	19.6
Versions	532	3.4	78	14.6	8.2
Breech	501	3.2	149	29.7	15.7
Sections	830	5.3	92	10.8	9.7
	15,507				

whose birth weights were under 4 pounds, while in the forceps group there were only 24 babies who weighed less than 4 pounds. In other words, it was not so much the method of delivery as it was the size and development of the child that gave us such a discrepancy in the mortality of these two methods of delivery. If the 251 babies weighing less than 4 pounds are eliminated from the spontaneous deliveries and the 24 similar babies eliminated from the forceps deliveries, the relative percentages are 3.2 and 2. The third lowest mortality rate, 10.8 per cent, occurred in the 830 deliveries by cesarean section. The fourth occurred in versions in which the mortality was 14.6 per cent. The highest mortality rate occurred in the 501 breech deliveries. Although this type of delivery made up only 3.2 per cent of the total deliveries, the mortality rate was 29.7 per cent.

The length of life of the 483 babies who died is analyzed in Table V. It is noted that 216, or 44.7 per cent, lived less than six hours. A fair number of cases did not make any attempt at respirations, but because their heart was beating when de-

TABLE V. LENGTH OF LIFE

Less than 6 hr.	216—44.7 per cent	
6 to 12 hr.	49—10.2 per cent	65.5 per cent
12 to 24 hr.	51—10.6 per cent	
Over 24 hr.	167—34.5 per cent	
Total	483—100 per cent	

livered, were classified as neonatal deaths and helped to increase the mortality in this group. Of the 483 neonatal deaths, 65.5 per cent lived less than twenty-four hours. Most of these babies who died in the first twenty-four hours were among

TOXEMIA

The influence of toxemia in the mother on the fetus is well known. Efforts are made either to control the condition or to deliver the baby as rapidly as possible in the severe cases. In this group there were 53 babies, or 11.4 per cent, of the stillbirths who died mainly because of toxemia in the mother; 25, or 5.4 per cent, of the neonatal deaths were in this group, or deaths of 78 babies (8.4 per cent) of the total mortality were ascribed to toxemia in the mother. In the 350 cases without autopsy, 9.4 per cent were ascribed to toxemia in the mother. In most of these cases in this group the primary cause of death was maternal; the secondary or fetal cause was in most cases one of prematurity.

MALFORMATIONS

Thirty years ago malformations caused about the same number of deaths as we find in this report. It can safely be said that there is a strong hereditary tendency in the development of malformations. Just what place the biochemical reactions of the mother have in causing malformations is unknown. There were 29 cases, or 6.2 per cent, of the stillbirths who died because of malformations; 41, or 8.4 per cent, of the neonatal deaths were ascribed to this cause. These 70 cases, or 7.5 per cent, of the total group were thought to have died from malformations. The malformations were usually multiple. They involved the nervous system, the heart, the intestines, the kidneys, either alone or in conjunction with some other condition. In most cases the malformations were inconsistent with life. Of the 350 cases without autopsy, 5.4 per cent of the deaths were ascribed to malformations.

ACUTE INFECTIONS

So far as could be determined, acute infections other than syphilis did not cause the death of any in the stillbirth group. There were 50, or 10.8 per cent, of the neonatal deaths that were due to infection, but when considered with the total deaths, infection was the cause of death in 5.2 per cent. Thirty-six of the infections, or 3.8 per cent, were due to pneumonia of one kind or another. It is our opinion that perhaps most of the infections that occur in the newborn, when sufficiently severe to cause death, are pretty well generalized and probably belong to the septic group. Careful bacteriologic studies before death and at autopsy will show even higher rates for infections. Of the 350 cases without autopsy, 3.7 per cent of the deaths were ascribed to infections. It is noted at autopsy that in nearly all of the cases of massive atelectasis, the lungs of these babies have a certain amount of inflammatory changes on microscopic examination, and are probably after all pneumonias. One case of peritonitis was due to a ruptured gastric ulcer. Two apparently were associated with congenital syphilis; 1 followed a profuse vaginal discharge which at autopsy showed severe pelvic inflammatory disease. Several of the cases of peritonitis followed attempts at reconstruction of malformations of the intestines. Practically all the cases of meningitis were associated with spina bifida, or with surgical attempts to correct the same. There was one case of meningitis which was due to the colon bacillus that was diagnosed several days before death.

Hemorrhage and hemorrhagic conditions are more frequent in the neonatal deaths than in the stillbirth group. Hemorrhage into the lungs, from rupture of the liver, and hemorrhage into the adrenal, are considered in this group although they might conceivably be placed in deaths due to trauma. There were 3, or 0.6 per cent, of the stillbirths that could be ascribed to hemorrhagic conditions, while there were 26, or 5.6 per cent, of the neonatal deaths that were due to hemorrhagic conditions. Sixteen babies died because of hemorrhage into the lungs, from the liver or adrenal, without any other definite evidence of hemorrhagic disease being present. Hemorrhagic disease itself was diagnosed only eight times, erythroblastosis twice, hydrops foetalis three times. Just what hemorrhagic disease of the newborn is has not yet been definitely established. During the past year such a diagnosis

was made in one child, who five months later had developed what appeared to be a typical case of aplastic anemia. Another so-called hemorrhagic disease of the newborn, at two years of age was a typical hemophiliac. Perhaps it would be well to place this group among the malformations, because it may represent a form of malformation of the blood forming organs. In the 350 cases without autopsy, hemorrhage and hemorrhagic conditions were the cause of 1.1 per cent of the deaths.

UNKNOWN CAUSES

There were 55, or 11.9 per cent, of the stillbirths in which no cause of death could be found. There were 24, or 5 per cent, of the neonatal deaths in which no cause of death could be found; that is, 79 of the total, or 8.4 per cent, belong

TABLE VII. PRIVATE CASE RECORD—SEVEN YEARS

Total cases	4,062
Deaths	98
Mortality per cent	2.4
Corrected mortality	40
Corrected mortality per cent	0.98
Autopsies	30

to the unknown group. It is difficult to decide whether a patient has died because of general debility, including prematurity, and should be placed in that group, or whether because of the term and weight of the child and other conditions incompatible with life, it should be put in the unknown group. It is purely a matter of personal opinion. Most of the cases in this group (65) did not have autopsies, and there was insufficient clinical evidence to be sure of the diagnosis. Of the 350 cases without autopsy 18.5 per cent belong in the unknown group.

MISCELLANEOUS

There was one child who died quite suddenly whose mother was diabetic. Perhaps this child died of hypoglycemia but the death was so sudden that correct laboratory tests could not be made and autopsy was refused. There were 18 babies in this miscellaneous group in which the cause of death was doubtful, but they are put in the unknown group or in one of the other general groups. It does not seem wise to have a miscellaneous group of causes of death; for example, there were 5 cases in which an enlarged thymus was found at autopsy and was ascribed as the cause of death. It is doubtful if this can ever be given as a definite cause of death. In 4 other cases there was some placental abnormality which might easily have been the cause of death. These 4 cases were put in the asphyxial group. Seven deaths in the miscellaneous group were caused by direct attempts at self-induced abortions.

COMMENT

Evidently the problem is a prenatal and natal one, and primarily must be solved by the obstetrician. However, there should be very close cooperation between the obstetric and pediatric staffs of all maternity hospitals. It has been our custom at the Philadelphia Lying-in Hospital to make the Pediatric Department responsible for the child as soon as it is born. In all difficult deliveries or other cases where the life of the baby is at stake, the pediatric resident is in attendance. In Philadelphia a general effort is being made through the committees on Maternal Mortality, Stillbirths, and Neonatal Deaths, to get as true a picture of the situation for the entire city as is possible. The committees are advocating adequate prenatal care, careful and complete clinical records, and

detailed autopsies on all deaths. It is hoped also that all the hospitals will institute discussions of their infant deaths before the pediatric and obstetric staffs.

Owing to the very nature of pregnancy, many difficulties are encountered in attempting to find a solution. The problem is a very complex one and will require intensive study. Hereditary influence, the lethal effects of toxins in the mother's blood, her own general health and age during pregnancy, together with her diet and nutrition, undoubtedly have definite effects on the growing fetus. The rate of growth of the fetus, especially during the first two months of pregnancy, is so rapid that cell division and differentiation of tissue constitute an immense hazard. It is no wonder that physiologic inadequacies do occur. The wonder is that they do not occur more often than we have been able to demonstrate. As most of the stillbirths and neonatal deaths are associated with prematurity, one cannot help wondering whether Mother Nature is allowing the spotted and stunted fruit to fall and perish early. However, after seeing numerous small premature infants grow and develop normally one cannot allow such an idea to enter into this problem of neonatal mortality. Many of the problems of this age period are undoubtedly on the borderline between physiology and pathology, and this will require careful biochemical studies to indicate the proper solution. Imperfect physiologic function plays a part, and perhaps a bigger part than we can conceive of at present.

Mortality rates vary considerably in different places, even though there seems to be a great similarity in nursery routine, method of feeding and general equipment. Postnatal care in such instances does not seem to be the answer. Perhaps it is the vitality of the groups in question which in turn is materially affected by maternal conditions, social and economic status, and obstetric procedures. So often our autopsy reports are completed with the statement that the cause of death is unknown. This fact points out the need for well-trained pathologists who will be willing to investigate minutely the structural changes in the organs of the newborn babies. Even this does not seem to offer much information regarding the functional ability of the various organs. Undoubtedly the spread of general health education, and better understanding of congenital syphilis and toxemia and their treatment, preventing accidents at birth, the prevention of and improved care of premature infants, will in turn have some influence on neonatal mortality.

SUMMARY AND CONCLUSIONS

1. A study of 944 infant deaths in a seven-year period at the Philadelphia Lying-in Hospital is presented.

2. Close cooperation of the obstetric and pediatric staffs is advisable.

3. Infant deaths should be reviewed at the monthly staff meetings. Errors in judgment and technique should be pointed out and responsibility fixed.

4. Skilled pathologists should perform the autopsies. Microscopic sections should be made and postmortem cultures taken.

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RETROPERITONEAL CYSTIC LYMPHANGIOMA

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IT HAS been our opportunity to study a case of retroperitoneal lymphangioma which we report because of its rarity and unusual size. This case, together with four collected from the literature by Kretschmer and Hibbs[1] to which they added one of their own and a case described by Sick,[2] bring the total number of such lymphangiomas to seven.

HISTORY OF CASE

Mrs. B., aged 32, entered the Colorado General Hospital on Feb. 26, 1935. Approximately four years previously she had noticed a growth in the abdomen which she described as being as large as the clenched fist. Six months later she was operated upon in one of the smaller Colorado towns. At this time the tumor was said to be as large as a football, and was believed to be a "carcinoma involving the large bowel, and inoperable." A small piece examined by a pathologist was reported as being benign. Following the operation the patient experienced a coughing seizure, the incision opened and a considerable discharge followed. Upon leaving the hospital she states that the tumor gradually increased in size to December, 1934, when she was given intravenous colloid gold. After which, growth was rapid, and though she thought she was losing flesh, she actually gained 14 pounds. She continued doing her housework, but with difficulty because of heaviness and the size of the abdomen. She was short of breath but experienced no actual pain. There was no swelling of the ankles.

About one week before presenting herself to us she began to have almost constant nausea; there was a slight elevation of temperature, with a feeling of malaise; the bowel and urinary functions were normal.

The patient's menstrual history was normal, she had had five children and one induced abortion. There was nothing else of importance in her history.

Physical Examination.—On admission there was a slight cough, and a fever varying from 100 to 102° F.; the pulse was 100 to 120.

The abdomen contained a large, firm, cystic-feeling tumor, nodular along its inferior margin, smooth over the anterior and upper surfaces. This projected over the symphysis pubis and extended above to the ensiform (Fig. 1). There was tympany in both flanks.

On pelvic examination the tumor could be felt at the brim of the pelvis, with a small uterus distinct from the growth above.

The urine was normal, the blood pressure 120/80. The red blood cell count was 3,520,000 with hemoglobin 11.5 gm. The leucocytes were 14,000 with 85 per cent polymorphonuclear leucocytes.

Operative Findings.—On opening the abdomen from the symphysis to 3 inches above the umbilicus, the tumor was seen to be retroperitoneal (Fig. 2). The transverse colon ran across the upper part of the growth and the small intestines were pushed to the sides and lay in the flanks. The posterior parietal peritoneum over the tumor was adherent to the peritoneum of the anterior abdominal wall in the right upper quadrant. These adhesions were fairly firm and were freed. The posterior parietal peritoneum over the tumor was opened in the midline, clamping the large vessels which ran in the retroperitoneal layer and communicated in places with those within the capsule of the tumor.



Fig. 1.—Patient prior to operation.

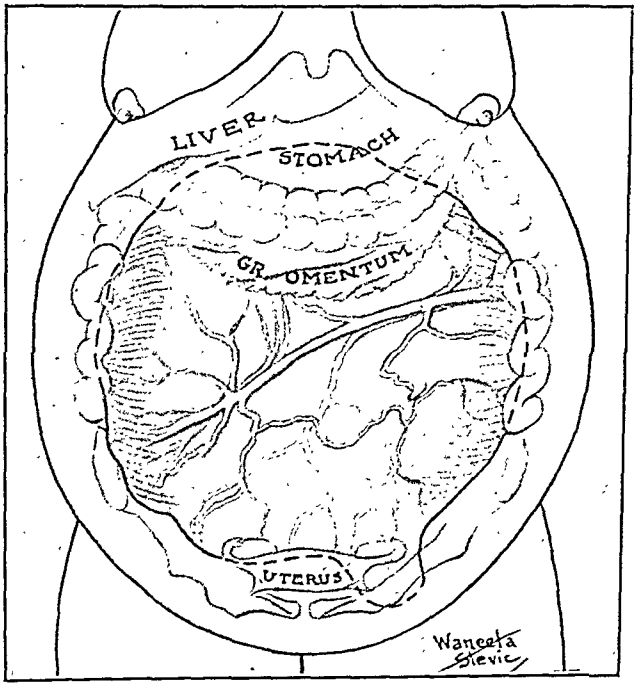


Fig. 2.—Retroperitoneal cystic lymphangioma. Schematic representation of position of tumor with anterior abdominal wall removed. Shaded area and dotted line indicate tumor.

The tumor was quite easily shelled out by blunt dissection with the hand. In the lower left portion of the abdominal cavity the projection shown in the photograph (Fig. 3) lay under the upper portion of the sigmoid and left broad ligament and extended to the abdominal opening of the inguinal canal. There was some bleeding in a few areas, but this practically ceased on removal of



Fig. 3.—Gross specimen, anterior surface, showing projection which extended to the left internal inguinal ring.

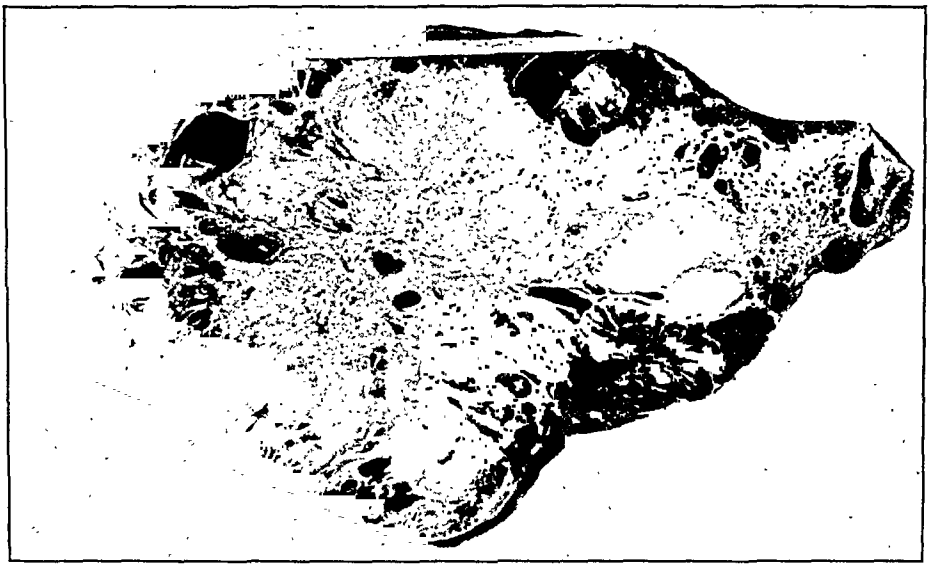


Fig. 4.—Cut surface of tumor after fixation.

the tumor. The peritoneum was sewn over, tying off the large vessels. The retroperitoneal cavity remained dry. The gall bladder, kidneys, uterus, tubes, and ovaries were grossly normal. The patient ran a temperature of 101° to 104° F. for five days with a pulse of 110 to 120. This subsided and was attributed to absorption from the large retroperitoneal space. The convalescence was subsequently normal and the patient left the hospital apparently well.

One year after operation the patient was in good health with no apparent recurrence of the tumor.

Gross Description.—The specimen was an elliptical-shaped mass of tissue with a rounded projection extending from the lower border. The mass measured 46 by 43 by 21 cm. (18 by 17 by 9 inches) and weighed 18 kilograms (40 pounds). The external surface was bluish red in color and smooth for the most part although there

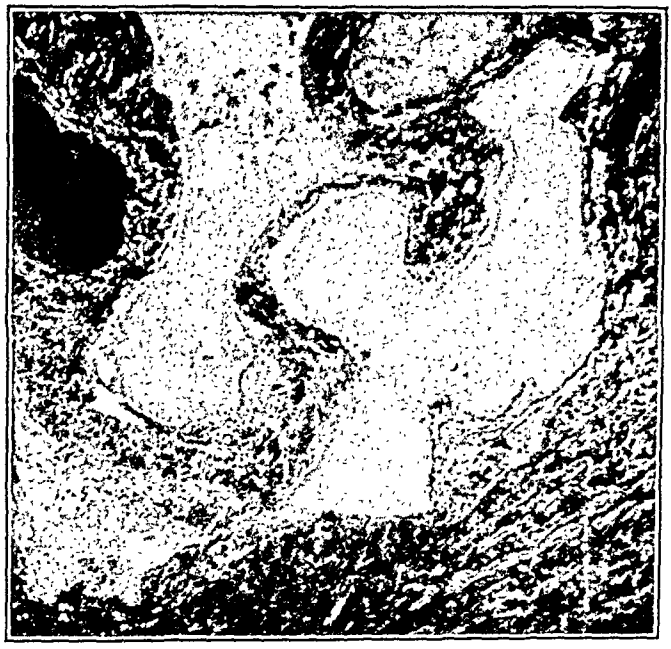


Fig. 5.—Photomicrograph of section of retroperitoneal lymphangioma showing large spaces (low power).

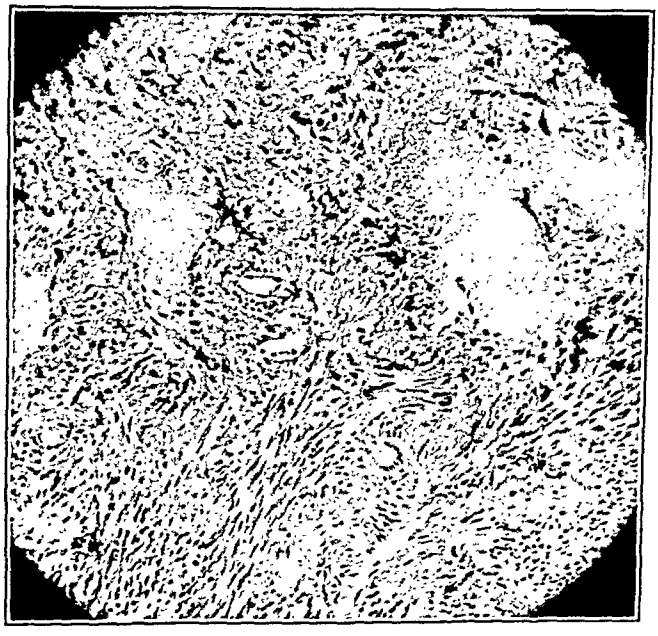


Fig. 6.—Photomicrograph of section of tumor showing smooth muscle fibers (high power).

were adherent tags of connective tissue. From the surface projected a number of low rounded lobulations measuring from 8 to 2 cm. in diameter (Fig. 3). Beneath the surface were numerous blood vessels, some of which measured 0.5 cm. in diameter. These stood out like blue cords. The mass had a semisolid consistency and was apparently cystic in structure.

The specimen was opened by a longitudinal incision along its greatest diameter. When sectioned, a serous blood-tinged fluid poured forth from numerous cystic cavities. None of this fluid was mucinous or coagulated. The cystic spaces ranged in size from 8 cm. down to microscopic dimensions, the majority being 0.5 to 1.0 cm. in diameter (Fig. 4). They had smooth gray glistening walls and some of them communicated with one another while others appeared as solitary spaces. The spaces, for the most part were located on the periphery of the mass, giving it a honeycombed appearance while the center was occupied by a more solid mass of tissue, the cut surface of which was purplish white with gray trabeculations. A comparatively small number of cystic spaces were seen in the central area.

Microscopic Examination.—The tumor consisted of numerous spaces of all conceivable sizes and shapes. These spaces contained a finely granular eosin-staining precipitate. A few spaces contained red blood cells, all of which gravitated to one side of the spaces (Fig. 5). The lining of each space was a layer of flattened endothelial cells with small oval and spindle-shaped granular nuclei. The wall between some of the larger spaces was composed of a very thin layer of fibrous connective tissue. Other spaces were separated by a thick layer of edematous fibrous connective tissue which contained bundles of smooth muscle fibers and collections of lymphocytes (Fig. 6). The blood vessels were not numerous. They were congested, dilated, and had poorly developed muscular walls. The more solid mass of the tumor was composed of bundles of fibrous connective tissue and smooth muscle which resembled uterine muscle in structure and arrangement. There was some hyalinization of the fibrous connective tissue throughout these areas as well as slight lymphocytic infiltration and edema.

Pathologic Diagnosis.—Retroperitoneal cystic lymphangioma.

REVIEW OF THE LITERATURE

Kretschmer and Hibbs[1] in 1934 reviewed the literature on retroperitoneal lymphangiomas and summarized the previous cases. They included four cases to which they added one of their own. That the extreme rarity of this condition might be questioned was mentioned by these authors and also McFadden.[3] Retroperitoneal cysts, thought to have been derived from the urogenital ridge or from misplaced peritoneal cells are described more frequently. Warfield,[4] discussing mesenteric and retroperitoneal cysts of various types, estimated that 400 such cysts have been reported. McFadden,[3] who reported a retroperitoneal lymphangioma, said, "Looking over the published papers and the description of cases, this case suggests that retroperitoneal cysts are true lymphangiomas and not cysts arising from local peritoneal cells or from cells derived from the urogenital ridge."

Makins[5] is also of the opinion that most mesenteric and retroperitoneal cysts are lymphangiomas. Ewing[6] devoted a paragraph to retroperitoneal lymphangioma and made no mention of the rarity of the condition.

On the other hand, Sick[2] described a case of multiple retroperitoneal lymphangioma and made no mention of any previous cases. Gaudier and Gorse[7] (quoting Kretschmer and Hibbs[1]) reported a retroperitoneal cystic lymphangioma and drew attention to the fact that diligent search of the literature revealed no strictly analogous case. Westman[8] reported a retrocecal lymphangioma and Burhaneddin[9] a multilocular cystic retroperitoneal lymphangioma. Both of these authors could find no similar cases in the literature.

Reviewing all types of retroperitoneal tumors Magoun,[10] Andrews,[11] and Schmid[12] did not include any cases of retroperitoneal lymphangiomas. Schmid,[12] who collected 297 cases of retroperitoneal tumors, stated that, "Cysts of varied types are rarely seen."

Until the nature of mesenteric and retroperitoneal cysts, thought to be derived from the urogenital ridge and peritoneal cells, is determined, we prefer to believe that retroperitoneal lymphangiomas are rare, and add our case to the six previously described.

Pathology.—Kaufmann[13] described lymphangiomas as variously shaped, diffuse or circumscribed neoplasms, the chief constituents of which are spaces lined with

endothelium and containing lymph. These spaces in some cases are enormously distended and in others the walls are remarkably thickened. For purposes of classification the original description of lymphangiomas by Wegner was followed by Kaufmann.[13] Wegner divided lymphangiomas into (a) simple lymphangiomas, usually situated superficially in the skin, (b) cavernous lymphangiomas, found chiefly in macroglossia, macrocheilia, and more rarely in other parts of the face and skin, (c) cystic lymphangiomas, consisting of cysts, simple or subdivided, lined with endothelium, the contents of which are clear, serous, milky, or chocolate-colored fluids which may contain cholesterin and detritus. These tumors appear chiefly in the neck, breast, axilla, lower sacral region, abdomen, thighs, and inguinal regions. When located in the mesentery they often contain chyle, in which case they are called chylangiomas.

The majority of authors are inclined to believe that these tumors arise from misplaced embryonal lymphatic tissue. Ewing[6] believed they are probably of embryogenic origin. Thompson and Keiller,[14] discussing the etiology of lymphangioma of the neck, traced the embryologic development of the lymphatic system and believed these tumors arise from embryonic rests, the sites of predilection being the neck and the region of the iliac vessels because the anlage of the lymphatic system appears in these areas.

One other factor believed to be important in the development of these tumors is passive dilatation with hyperplasia of the pre-existing lymph vessels (lymphangiectasis). Schmid[12] quoting Kaufmann[13] thought that lymph stasis plays an important part, leading finally to muscle hypertrophy and tumor formation. Ewing,[6] however, was able to demonstrate free communication between afferent and efferent vessels in several lymphangiomas and concluded that stasis could not have been present in these cases. Kretschmer and Hibbs[1] mentioned the fact that lymphangiomas, which are true neoplasms, and lymphangiectasis are separated from one another with difficulty at times and emphasized that a sharp differentiation should be made between the two conditions.

Concerning the enlargement of lymphangiomas, proliferating buds of endothelium forming new lymph vessels have been fully recognized in certain cases (Ewing[6] and Kretschmer and Hibbs[1]). That this is not entirely the case has also been brought out by Ewing[6] who stated that in some of the largest cystic lymphangiomas the signs of neoplasm are the least distinct. Thompson and Keiller[14] postulated that the endothelium under certain conditions may secrete fluid and that due to some alteration in the permeability of the vessel wall little of the fluid is reabsorbed with resultant cyst formation and tumor enlargement. In Sick's[2] case, one of the retroperitoneal cysts was marsupialized, and at various times during the day there was a marked increase in the amount of watery secretion.

The pathologic reports of the previous cases of retroperitoneal lymphangioma, except that of Sick,[2] have been adequately summarized by Kretschmer and Hibbs.[1] Sick's[2] case is significant enough to be reported more fully in this paper. At autopsy two large cysts were encountered on examination of the peritoneal cavity. The largest was located in the left upper quadrant near the jejunoduodenal juncture. A small spherical cyst, measuring 8 cm. across, was located on the right side below the kidney and above the brim of the pelvis. When the small intestines were removed, a cushionlike mass of retroperitoneal cystic spaces with a nodular firm consistency was encountered. It partially covered the pancreas and kidneys and extended down to the promontory of the sacrum. The ascending colon was pushed forward and to the side, the mesenteric attachment of the small intestines up and towards the liver. This mass was most marked on the right side of the abdomen and gradually blended with normal retroperitoneal tissue on the left.

Microscopically the tumor consisted of slitlike spaces lined with characteristic endothelium. The stroma of the larger spaces had bundles of smooth muscle which in instances formed an almost continuous wall about the space. In the connective tissue there was infiltration with plasma cells, lymphocytes, and mast cells. Many of the spaces contained cholesterin.

Retroperitoneal lymphangiomas vary markedly in size and shape. The largest heretofore reported was Burhaneddin's[9] case. This tumor measured 45 by 30 cm. (18 by 14 inches), and weighed 6.4 kilograms (14 pounds). The smallest tumor, Westman's[8] case, was the size of a clenched fist.

Of the seven retroperitoneal lymphangiomas (including ours), four were located on the right side of the spinal column. Sick's[2] case was predominantly right sided. The remaining two occupied the space on both sides of the spine. Three of the tumors had fingerlike projections to or into the inguinal rings. Two were located on the right and one on the left side.

All of the lymphangiomas were cystic in nature, the size of the cysts varying from 8 cm. to microscopic dimensions. The fluid in the cystic spaces, mentioned in three cases, was chocolate colored in two, clear in one. Cholesterin was mentioned in Sick's[2] case, and after fixation, a gelatin-like substance containing homogenous opaque yellow-brown material in its center was noted by Kretschmer and Hibbs.[1]

Microscopically evidence of malignancy was found only once in the series. Kretschmer and Hibbs[1] found the endothelial lining of many of the cysts to be hyperplastic in nature. No mitotic figures were seen.

The stroma of these tumors was found to contain smooth muscle in 3 cases, Sick's,[2] McFadden's[3] and ours. The stroma of Kretschmer and Hibbs[1] case was made up of fibrous connective tissue undergoing atrophy and hyalin degeneration. Lymphoid tissue having a lymph node arrangement was observed by McFadden.[3] Several collections of lymphocytes were found in our case. Kaufmann[13] mentioned that the fibrous connective tissue stroma may partake in the neoplastic growth of true lymphangiomas and at times may overshadow the endothelial proliferation, in which case it is proper to call the tumor a lymphangiofibroma. The tumor in our case showed a predominance of smooth muscle in many areas and might justifiably be classed as a retroperitoneal lymphangioliomyoma.

DISCUSSION

While cystic lymphangioma is fairly common, the occurrence of these tumors in the retroperitoneal space is, to the extent of our knowledge, rare. There is some confusion in the literature as to the pathologic nature of retroperitoneal cysts. We feel that this phase of the subject should be clarified. The cases referred to and reported in this paper are all cystic lymphangiomas and may be of some help in the subsequent classification of these tumors.

SUMMARY

A case of retroperitoneal lymphangioma is reported in detail. Five cases have been summarized by Kretschmer and Hibbs.[1] To this number we have added a case described by Sick,[2] bringing with our own, the total number of such cases to seven. To our knowledge there is nothing characteristic about such tumors whereby they may be diagnosed prior to operation. Of the seven cases reported, five patients have survived operation successfully.

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POST-PARTUM HEMORRHAGE AS A CAUSE OF DEATH*

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THE purpose of this study is to analyze the etiology and details of various methods of treatment as shown by the records of 52 deaths from post-partum hemorrhage in the 183,384 deliveries in Philadelphia, over a six-year period, 1931 through 1936. Post-partum hemorrhage was the direct cause of death in 52 cases, 0.028 per cent, or once in every 3,527 labors. These figures are similar to those quoted by Williams,[1] "Fatal hemorrhage is fortunately rare, having occurred in 0.03 per cent or once in 3,121 times." The Maternal Welfare Committee of the Philadelphia County Medical Society judged 32, 61.5 per cent, of these deaths as preventable. The responsibility for 28 deaths, 53 per cent, was assigned to the attendant, as treatment in all was deficient. Four of the fatalities, 7.5 per cent, were due to ignorance of the patients; while 20, 38 per cent, were termed nonpreventable. All else passes into insignificance before the fact that the Committee felt over one-half of the deaths were preventable.

Forty-one patients in this series, 79 per cent, were delivered in hospitals, while 4, 7.6 per cent, of those delivered at home were taken to the hospital after the complication developed. Three of the patients were attended by midwives who called in physicians when the post-partum hemorrhage occurred. Medical students were in attendance on 3 cases, 2 of which were hospitalized and the third lived eight hours while the student tried to get some one to come to his aid.

The incidence of spontaneous deliveries in this series of post-partum hemorrhage cases is 42.3 per cent, contrasted with an average of 72 per cent in all births, as shown by the first "three-year study" in Philadelphia. The incidence of version, 15.4 per cent, in this series is ten times as high as the average incidence of version in the hospital deliveries of the City in the first three years of this study, 1.52 per cent. Indications for the operative interference were not made clear, and two history charts carried the notation of "elective version."

In our consideration of treatment in these cases it is well that we know the interval of time between delivery and death of the mother. Is there time for adequate treatment once this accident has occurred? Here we find our most variable figures, since death came anywhere from one and a half hours up to seventeen days following delivery. To arrive at a time interval, we excluded 4 cases from the average, since this accident, for the most part, shortly follows labor and not several days later. These 4 cases will be considered separately as late post-partum hemorrhage.

The usual story was not that of sharp, marked hemorrhage for a few minutes and then sudden death. Rather the picture brought to light by this study was one of steady moderate bleeding over a period of several hours, ending in shock and death because no one became

*Read before the Philadelphia Obstetrical Society, March 3, 1938.

alarmed. There was an occasional case where bleeding was sudden and great in volume, with the patient going into shock rapidly, but even in such a case there was usually time for adequate treatment. Thus we find the average time between delivery and death of the mother, as five hours and twenty minutes. Only 6 patients, 11.5 per cent, died within two hours of delivery and none in less than one and a half hours. In the vast majority of cases there was adequate time for very intensive treatment. A fairly typical case is the following:

This patient was delivered at home by her physician, assisted by a nurse. Labor was easy and uncomplicated. The placenta was not expelled and since there was no alarming hemorrhage, nothing was done except watchful waiting. Bleeding was described as "constant seepage," and four hours after delivery she was admitted to the hospital in shock. General supportive treatment and intravenous saline were administered. No attempt was made to deliver the placenta, since the patient was "not bleeding a great deal." However, she died in shock seven hours and forty minutes after delivery.

The causes of bleeding in this series were variable. In 27 cases hemorrhage was due to either retained placenta (14), abruptio placentae (7), or inertia uteri (6). Fourteen patients were classed as "unexplained," since their histories gave no clue as to the condition of the uterus while bleeding was going on. We might well infer, since no apparent cause was given and the patient continued to bleed, that we were dealing with inertia uteri. This inference might or might not be true, consequently we assigned no cause. Table I gives the etiologic factors involved in the entire series. Toxemias of pregnancy were associated as contributory causes in six deaths. Pre-eclampsia appeared in 3 cases, eclampsia, nephritic toxemia and an ill-defined type (low blood pressure), each once.

TABLE I. ETIOLOGY, PERCENTAGE DISTRIBUTION

Retained placentas	26.9 per cent
Abruptio placentae	13.4 per cent
Inertia	11.5 per cent
Lacerated cervix, lacerated perineum	3.8 per cent
Uterine fibroids	3.8 per cent
Partial placenta previa	3.8 per cent
Purpura hemorrhagica	1.9 per cent
"Lacerated uterus"	1.9 per cent
Retained placentas, lacerated perineum, cervix and uterus	1.9 per cent
Unexplained	26.9 per cent

Methods employed in the treatment of post-partum hemorrhage were often haphazard and lacking in uniformity. Uterine packing was employed in only 28 cases. Notwithstanding the fact that bleeding continued through the packing in most instances, only 12 were repacked. Vaginal packing alone was employed in 3 cases for uterine bleeding. In this respect, let us consider a case report:

To hasten delivery, a physician used two ampoules of pituitary solution. Following the birth of the baby, ergot was given by mouth. The placenta was adherent

so the physician packed the vagina. Six hours later the patient had a severe hemorrhage. The vagina was packed again, the bleeding continued, and she died nine hours and twenty minutes after delivery.

Six of the 14 retained placentas were manually removed and the uteri packed. No reasons were given as to the cause of retention and no mention was made of placenta accreta. Traditional treatment for retained placenta is manual removal, yet 7 died without any attempt at completion of the third stage of labor.

The most common therapeutic measure employed was intravenous fluid. Thirty-six patients, 69.2 per cent, were given parenteral fluid either in the form of physiologic saline or in combination with glucose. Pituitary solution and some form of ergot found use in 48 per cent of all cases. Only 30 per cent of the patients received blood transfusions. This is most regrettable since 79 per cent of the deaths were hospital deliveries. More appalling is the discovery that eight patients, 15.3 per cent, went into shock and death with apparently no attempt at treatment. The following case report is only to illustrate that "it can happen here":

This patient entered the hospital in active labor. The "head was found to be engaged and the cervix four fingers dilated." The membranes were unruptured. Because of "dystocia" three minims of pituitary solution were given, following which, the membranes ruptured. Shortly thereafter, high forceps were applied and the baby was extracted with difficulty. This procedure resulted in a complete perineal tear and "bilateral lacerations of the uterus." A part of the placenta was left in. There was no record of therapy employed or even an attempted repair. The patient was taken from the delivery room in shock and still bleeding profusely. Death occurred two hours and forty minutes after delivery.

Hot intrauterine douches were used without advantage in two cases, while hysterectomy in three proved to be of little help. To illustrate this last named procedure, let us consider the following case:

This patient developed pre-eclampsia and was hospitalized. For two days she received active treatment and improved. Next she was given a medical induction of labor and delivered spontaneously with no difficulty. Ten minutes later the placenta came away spontaneously. Twenty minutes later the patient began to bleed freely and despite adequate doses of oxytocics, the uterus would not contract. She was packed with gauze, but the bleeding continued through the tampon. An intravenous infusion was started while the patient was wheeled to the operating room, where a hysterectomy was done. More intravenous fluids were administered and a 500 c.c. blood transfusion was given. Notwithstanding prompt and efficient treatment, the patient died four hours after delivery.

Late post-partum hemorrhage was fatal to 4 women in this series. All had retained secundines, while one developed puerperal sepsis, but died of hemorrhage on the seventeenth day. Three patients died eight, ten, and twelve days following delivery; only in one instance was an attempt made to evacuate the uterus. Table II presents the various treatment methods used in these cases. In the light of retrospection, let us bear in mind that we do not know how many women with post-partum hemorrhage were successfully treated with the very same procedures employed here with failure.

It is hardly expedient to discuss treatment without having first considered prophylaxis. Prevention of post-partum hemorrhage begins in the prenatal period, with physical conditioning of the patient,

paying particular attention to her nutrition. All foci of infection should be eliminated and any existing anemia treated. A history of a previous post-partum hemorrhage, or where fibroids are present, or any condition causing overdistention of the uterus, should indicate a blood typing for that patient. In short, the pregnant woman should have the benefit of close medical study throughout her prenatal period, so as to give her ideal preparation for delivery. When labor commences, precaution against a developing inertia uteri is most important. Adequate and judicious sedation, nourishment, either oral or parenteral, are measures of paramount importance.

Proper management of the third stage of labor is most important. A procedure of definite prophylactic value is the administration of 1 c.c. of pituitary solution and 1 c.c. of aseptic ergot, as soon as the second stage of labor is completed, thus allowing the placenta to be expelled with little or no massage. We made mention of this[2] as a matter of routine, and Adair did not agree with us stating,[3] "that the routine use of any oxytocics during the third stage of labor is undesirable as it is likely to cause perversion of the normal mechanism." The normal mechanism is for the uterus to be left alone to contract and expel its placenta, but in most clinics it consists in the operator or the nurse massaging the uterus into contraction, expressing a placenta frequently not completely separated. Certainly this must be a traumatic procedure and it logically follows that post-partum hemorrhage might very well develop from such maltreatment. On the other hand, the oxytocics described when employed will contract the uterus with as little damage as possible and keep it contracted. Only rarely is one required to do a forceful expression. Many question this procedure, feeling that oxytocics following the birth of the baby will cause retained placentas. Here again we are able to say that such a complication has not been noted. However, Davis, Adair and Pearl[4] disagree, holding the opposite view that such a course "may eventuate in a post-partum hemorrhage" since it "may cause a contraction zone at the lower uterine segment, resulting in incarceration of a partially or incompletely separated placenta." The results we have seen do not support this contention. We know that the lower uterine segment is passive in its action, and should it contract it would be feeble at best. Schumann has had the above plan in operation for six years at the Kensington Hospital for Women, with a resultant extremely low incidence of even alarming blood loss, and it has proved to be a most helpful prophylactic measure.

In the treatment of post-partum hemorrhage two procedures stand out above all others; early transfusion and packing. At the first sign of abnormal amounts of bleeding, donors should be procured and held in readiness. In face of hemorrhage, thorough search should be made for lacerations in the body of the uterus (particularly after version), the cervix and the vagina, and these should be treated appropriately, either hysterectomy, repair, or packing.

TABLE II. FORMS OF TREATMENT EMPLOYED IN THIS SERIES
PERCENTAGE DISTRIBUTION

Intravenous fluids	69.0 per cent
Oxytocics	48.0 per cent
Placentas manually removed	46.0 per cent
Uterine packing	44.0 per cent
Blood transfusion	30.0 per cent
Repacked	23.0 per cent
Uterovaginal packing	9.6 per cent
Vaginal packing	5.7 per cent
Hysterectomy	5.7 per cent
Hot douches	3.8 per cent
No treatment	15.3 per cent

If the placenta has not already been delivered, it should be manually removed, and the removal followed by intrauterine and vaginal packing. The most satisfactory pack is one completely filling the uterus in a firm manner, following through to the vaginal outlet. Particular attention should be paid to the lateral fornices of the vagina where a well-placed pack will help to cut down the uterine blood supply. Should the bleeding continue through the packing, the uterus and vagina may be repacked, at least where technique was questionable the first time.

Ergonovine either intravenously, hypodermically, or rectally instilled is a valuable aid in contracting a uterus but cannot be relied on to the exclusion of the other steps mentioned.

Until blood donors are available, one of the easiest and most useful measures to be employed is intravenous fluid, either in the form of glucose and saline, gum acacia, saline or Ringer's solution. It found employment in 69 per cent of the cases, and we could see little reason why it was not used in 100 per cent of the patients. The intrinsic value of saline intravenously has long since been proved as an aid in combating hemorrhage and shock.

The difficulties encountered in securing proper donors for emergency transfusions is well known. However, a "blood bank" in every hospital would offset such difficulties. This blood supply may come from the hospital personnel or better, the plan recently proposed by Goodall, Anderson, Altimas and MacPhail. A preliminary report by Goodall and others shows fetal cord blood collected under aseptic conditions to be an "inexhaustible source of blood for transfusion, preserved at a minimum of cost, and preservable in its usefulness as a transfusion medium for at least sixty days." It must be remembered in transfusions for post-partum hemorrhage that blood must be replaced in amounts lost. Beck in his text tells of a patient needing 2,500 c.c. of blood to save life after a post-partum hemorrhage.

Hysterectomy is the most heroic treatment for post-partum hemorrhage. It should be held for the exceedingly small group of cases where everything possible is done and yet the patient continues to bleed. If one were to treat a patient wherein all lacerations had been

sutured, uterus and vagina packed, and repacked, if necessary, transfusion and intravenous fluids had kept the patient in fairly good condition and yet the bleeding persisted, hysterectomy would be the treatment of choice.

COMMENT

In this brief report we would like to call attention again to the judgment of the Maternal Welfare Committee of Philadelphia in terming 53 per cent of such deaths as preventable, with the responsibility assigned to the attendant. We have found the average time between delivery and death of the mother from hemorrhage to be five hours and twenty minutes, yet only one-half were packed and less than one-third had blood transfusions. Very few cases indicated anything but a haphazard plan of treatment. We have outlined accepted steps in the treatment of postpartum hemorrhage, all of which are within the scope of any modern hospital and staff.

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DISCUSSION

DR. THADDEUS MONTGOMERY.—Retention of the placenta is responsible for the largest number of maternal deaths in the series. This requires special attention.

Even in normal spontaneous delivery difficulties with the placental stage constitute a major hazard in the etiology of post-partum hemorrhage, particularly if the attendant is lacking in practical experience. Thus several of the deaths have occurred in spontaneous delivery inaugurated in the home—the attendant having had difficulty in expressing the secundines and his efforts having served perhaps only partially to detach the placenta.

With the wide acceptance of operative delivery, median episiotomy, immediate repair, deep analgesia and anesthesia, the hazards of this complication have been vastly increased. The effects of deep analgesia and of surgical anesthesia for delivery reveal themselves principally in the third stage, and unless the operator is very much on his guard he will very suddenly find himself in difficulty.

Of very great importance is the estimation of the patient's condition at the immediate conclusion of the delivery of the baby. If the condition is not good, it is imperative that further surgery be abandoned for the time, that all reparative work be postponed, and if bleeding is present, the uterus be promptly emptied and packed.

For myself, I much prefer to stop the anesthetic at the conclusion of the second stage and attend solely to the resuscitation and treatment of the baby and the management of the placental delivery. When the placenta is completely delivered, the uterus firmly contracted, and the patient's condition found to be excellent, the repair work, under further anesthesia, may be proceeded with.

This makes of the management of labor two separate steps, the first of which, the delivery, is to be entirely completed (child, placenta, and membranes) before proceeding with the second, the repair. The second step is never undertaken until it is certain that the patient has successfully and safely completed the first.

DR. J. C. HIRST.—I was very much interested in reviewing the statistics reported by Dr. Beecham to note that in these deaths from hemorrhage there were five sets of twins reported, an extremely high proportion. Multiple pregnancy is thus a predisposing factor to hemorrhage.

DR. CARL HENRY DAVIS.—It has been my belief for years that when the uterus is much overdistended, regardless of the cause, there usually is more bleeding post partum.

While Dr. Beecham's discussion of treatment was excellent, no mention was made of the Trendelenburg position for patients who are in shock from the loss of blood. If the patient is placed in this position and given oxygen, it may be possible to prevent damage to the brain during the interval which usually elapses before adequate blood can be secured by means of transfusion.

I do not like to introduce large amounts of fluid into the circulatory system until the bleeding has been stopped by appropriate means. It is probable that some patients have been lost through premature introduction of fluids.

DR. JOHN A. SHARKEY.—Version, and version and craniotomy accounted for 17.3 per cent of 52 deaths. In the first Philadelphia survey, version had a mortality of 6 per cent; in the same survey the cesarean section mortality was 5.5 per cent. In 22 of the version deaths the uterus was ruptured. It would be interesting to know whether or not these versions were done by experienced operators, in order that we may properly decide whether version is slightly more dangerous than cesarean section.

For several years we have been using pituitrin and ergot intramuscularly immediately after the baby is born and agree with Dr. Beecham that it materially reduces the amount of post-partum bleeding. Occasionally we have noted with this technique that the placenta becomes imprisoned in the lower uterine segment or cervix but one has only to wait about fifteen minutes for relaxation to occur. In addition if there is more than what we consider normal bleeding we give ergonovine intravenously and have found it very useful. However, in certain cases all of these measures will fail and packing of the uterus must be done. It is hard to understand why only 44 per cent of these patients were packed since this alone is perhaps the best single remedy we have for the control of post-partum hemorrhage, assuming of course that lacerations of the vagina and cervix have been properly treated. There were 23 per cent of these cases repacked. We feel that, when a uterus has been packed and repacked and still continues to bleed, hysterectomy should be done, leaving the second packing in the uterus until one is ready to open the abdomen. Certainly it would seem that, in patients with placenta previa and abruptio placentae who continue to bleed, hysterectomy should be considered; not, however, until the patient has been given some blood and allowed to recover partially from her shock. She should have more blood transfusions again after the uterus is out.

From Table II one might assume from the number of saline infusions as compared to blood transfusions, that the former were held to be the more valuable, since they were used in 69 per cent of the cases as against 30 per cent for blood transfusions. The exact reverse of this is actually true. We feel that blood transfusions should have been given in 100 per cent of the cases in this series since the average time between delivery and death was five hours and twenty minutes. With the inauguration of "blood banks" in various hospitals, no woman should die of post-partum hemorrhage after hospital delivery in Philadelphia without having been transfused with blood in sufficient amount.

INHIBITING EFFECT OF PENTAVALENT ARSENICALS UPON TRICHOMONAS*

Comparative Efficacy and Toxicity of Acetarsone, Carbarsone and Aldarsone in Laboratory Studies

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THE employment of pentavalent arsenicals for the treatment of trichomonad infestations is becoming more prevalent. For freeing laboratory animals from intestinal infestations with trichomonads, carbarsone has been used by Hegner and Eskridge[1] and by Gabaldon,[2] while acetarsone has occasionally been administered to human beings for this purpose.[3]

The three drugs in this group which have been recommended as trichomonadicides are acetarsone (3-acetylamino-4-hydroxy-phenyl-arsonic acid), carbarsone (p-carbamino-phenyl-arsonic acid) and aldarsone (sodium-methylene-sulfon-amino-hydroxy-phenyl-arsonate).[4] Comparative chemotherapeutic studies of the three arsenical preparations have not been reported, although a few clinical and laboratory observations concerning the effect of these preparations upon trichomonads or trichomonad infestations are available. In an earlier study Bland and Rakoff[5] gave comparative results of the killing effect of acetarsone and aldarsone on vaginal trichomonads and their relative efficacy in the treatment of vaginal trichomoniasis.

Several methods have been described for testing the effect of drugs upon trichomonads in vitro, depending upon the nature of the preparation and whether killing or inhibiting concentrations were sought. Generally such studies are complicated by the following technical difficulties: (a) inability to obtain bacteria-free cultures of trichomonads; (b) the limited solubility of some of the drugs tested; (c) osmotic pressure effects on trichomonads where high concentrations of salts were used; (d) the inhibiting effect of metabolic products of trichomonads and bacteria upon the organisms and the drug.

The present study of the chemotherapeutic efficacy of aldarsone, acetarsone, and carbarsone is based upon their relative inhibiting effects upon trichomonads in vitro and their relative toxicity. The inhibiting or trichomonadostatic values were determined by finding the lowest concentration of drug in culture media which prevented the growth of the flagellates. These included *Trichomonas hominis, T. vaginalis,* and *T. buccalis* from the bowel, vagina, and mouth of human beings,

*The writer is indebted to Dr. P. Brooke Bland and Dr. Norris W. Vaux for the facilities of their department and their constant interest during the course of this study.

respectively, and a cultivable trichomonad from the feces of a white rat, probably *T. parva*. The toxicity of the drugs was based on the maximum tolerated dose per kilogram when given to white rats per os.

TOXICITY STUDIES

Materials and Methods.—A comparative study was made of the toxicity of the three arsenicals. For purposes of this study the drugs were given per os since in the treatment of trichomonas infestations the drug is applied to mucous membrane surfaces such as the intestine or vagina.

A total of 87 healthy white rats were employed. The animals were under observation for a number of days before and at least twenty-one days after treatment. Each animal was weighed just prior to use and the dose was administered per kilogram of body weight. A solution of the drug to be tested was introduced into the stomach of the animal by means of a syringe and a piece of a fine ureteral catheter passed well into the esophagus of the rat.

TABLE I. TOXICITY OF ALDARSONE, ACETARSONE AND CARBARSONE PER OS IN RATS

DRUG	DOSE IN GRAMS PER KILOGRAM BODY WEIGHT	NUMBER OF ANIMALS	RESULTS	
			DIED*	SURVIVED**
Aldarsone (Aqueous solution)	1	1	0	1
	2	1	0	1
	3	1	0	1
	4	1	0	1
	5	1	0	1
	6	5	0	5
	8	6	1	5
	10	2	2†	0
	12	1	1	0
	15	1	1	0
Acetarsone (Acetarsone soluble—Abbott. Carbonated 0.7 gm. per gm. acetarsone)	2	1	0	1
	3	5	0	5
	4	5	3	2
	5	5	5	0
	6	2	2	0
	8	2	2	0
	10	1	1	0
Carbarsone (Carbonate 0.5 gm. per gm. of carbarsone)	3.0	2	0	2
	4.0	4	0	4
	5.0	5	1	4
	6.0	5	4‡	1
	6.5	5	4	1
	7.0	3	3	0
(Carbonate 1 gm. per gm. of carbarsone)	2	2	0	2
	3	2	0	2
	4	4	1	3
	5	3	3	0
	6	3	3	3
(Carbonate in excess)§	1	1	0	1
	2	1	0	1
	3	1	1	0
	4	1	1	0
	5	1	1	0

*Animals died within twenty-four hours unless otherwise indicated.

**Observed for at least twenty-one days.

†One died on second day.

‡One died on third day, another on fifth day.

§Exact amount not known but in excess of 1 gm. of carbonate per gm. of carbarsone.

To avoid the administration of large quantities the drugs were given in 10 to 20 per cent solution.

Aldarsone was used in aqueous solution since it is very soluble. Acetarsone was given in carbonated solution as acetarsone soluble* which contains 0.7 gm. of sodium carbonate per gram of acetarsone.

Carbarsone was used with several concentrations of sodium carbonate since early in the study it was observed that the proportion of carbonate materially influenced the toxicity of the preparation.

Results.—Table I shows that aldarsone was tolerated better than the other compounds. The maximum tolerated dose was in excess of 6 gm. per kilogram of body weight, and only 1 of 6 animals succumbed after receiving 8 gm. per kilogram.

The maximum tolerated dose of acetarsone soluble was less than 4 gm. per kilogram, since this amount was tolerated by only 2 of 5 rats; none of 5 rats succumbed after 3 gm. per kilogram.

Carbonated solutions of carbarsone did not yield entirely clear preparations, and for this reason various concentrations of sodium carbonate were tried. It was found, however, that the toxicity of the drug was increased by its addition. Thus with 0.5 gm. of carbonate per gram of carbarsone 4 of 5 rats tolerated 5 gm. per kilo and 1 of 5 rats tolerated 6 and 6.5 gm., respectively, while of 3 rats tested all succumbed to 7 gm. With equal parts of carbonate 5 gm. were not tolerated by any of 5 rats used, while 4 gm. were tolerated by 3 of 4 rats. When the carbonate was added in large excess only 2 gm. per kilogram were tolerated.

TRICHOMONADOSTATIC STUDIES

Materials and Methods.—The culture media employed routinely throughout the study consisted of Loeffler's dehydrated blood serum 0.4 per cent in a modified Ringer's solution (sodium chloride 6 gm., potassium chloride 0.1 gm., sodium bicarbonate 0.1 gm., calcium chloride 0.1 gm., distilled water 1,000 c.c.). The media were prepared fresh immediately before use. To quantities of culture media sufficient amounts of fresh stock solutions of the drugs were added to yield the desired concentration in the final mixture. The stock solutions of drugs were aldarsone 1 per cent in sterile distilled water, acetarsone 1 per cent in 1 per cent sodium bicarbonate solution, and carbarsone 1 per cent in 1 per cent sodium bicarbonate solution.

Ten cubic centimeters of the culture media-drug mixture were pipetted into culture tubes, which were then inoculated with 3 drops of active forty-eight-hour cultures of the flagellates. These were incubated at 37° C. and carefully examined for trichomonads at twenty-four-, forty-eight-, and seventy-two-hour periods.

The approximate concentration of each drug sufficient to prevent the growth of the flagellate tested was established after a number of trials, following which a series of ten concentrations closely graded on either side of the approximate value was prepared. These were similarly inoculated and examined. In this manner the concentrations of drug which just permitted and which just prevented growth were obtained. The latter was arbitrarily designated as the trichomonadostatic concentration, although the true value lies somewhere between the two.

Experiments were conducted on two strains of organisms for each of the four species of trichomonads studied; each experiment was performed three times.

Results.—In Table II are given the highest concentrations of drugs in which each strain of organisms tested survived, and the lowest concentration in which they were inhibited. It will be noted that in each experiment the required concentration of aldarsone was considerably lower than the respective figures for the other two drugs. The required concentrations of carbarsone were consistently slightly less than or equal to the acetarsone concentrations.

From the summarized results of Table III it will be seen that the average inhibiting or trichomonadostatic concentrations of aldarsone range from almost one-half to one-third that for acetarsone and carbarsone. Carbarsone in turn was slightly more effective than acetarsone.

*Acetarsone soluble is dispensed by the Dermatological Research Laboratories, Division of Abbott Laboratories, North Chicago, Ill.

Further examination of these tables indicates considerable variation in results not only among the trichomonads from the four different sources, but also among the two strains of each species studied; there was also moderate variation of the values for each experiment.

The lower values for *Trichomonas vaginalis* are in agreement with its general fragility in vitro; while the comparatively high figures for *Trichomonas parva* confirm our experience of the comparative resistance of this species to environmental factors, its easy cultivability and relative longevity in culture.

Those who have had experience in observing and cultivating trichomonads will not wonder at the variation in resistance of the two strains of each species tested. How much this is due to factors inherent in each strain of organism and how much to environmental factors, especially the accompanying bacteria, is difficult to estimate. The latter factor, however, is no doubt largely responsible for the variations in each set of readings for the same strain.

TABLE II. CONCENTRATIONS INHIBITING AND PERMITTING GROWTH

STRAIN	TESTS	ALDARSONE		ACETARSONE		CARBARSONE	
		ORGANISMS SURVIVED	ORGANISMS INHIBITED	ORGANISMS SURVIVED	ORGANISMS INHIBITED	ORGANISMS SURVIVED	ORGANISMS INHIBITED
		(CONCENTRATIONS IN MG. OF DRUG PER 100 C.C. CULTURE MEDIA)					
		Trichomonas vaginalis					
A	1	5.0	7.5	50	75	25	50
	2	5.0	7.5	50	75	25	50
	3	7.5	10.0	50	75	25	50
B	1	10	12.5	75	100	75	100
	2	25	50.0	100	125	75	100
	3	25	50.0	100	125	75	100
		Trichomonas hominis					
A	1	25	50	100	125	100	125
	2	25	50	150	175	150	175
	3	50	75	150	175	125	150
B	1	10	25	150	175	150	175
	2	25	50	75	100	75	100
	3	10	25	200	225	175	200
		Trichomonas buccalis					
A	1	25	50	75	100	50	75
	2	10	25	175	200	175	200
	3	50	75	150	175	100	125
B	1	50	75	175	200	75	100
	2	50	75	150	175	125	150
	3	75	100	200	225	150	175
		Trichomonas parva					
A	1	25	50	100	125	100	125
	2	50	75	150	175	125	150
	3	75	100	150	175	125	150
B	1	100	125	200	225	125	150
	2	75	100	225	250	200	225
	3	100	125	200	200	150	175

TABLE III. AVERAGE TRICHOMONADOSTATIC VALUES

	ALDARSONE (MG. PER CENT)	ACETARSONE (MG. PER CENT)	CARBARSONE (MG. PER CENT)
T. vaginalis	45	96	75
T. hominis	46	163	154
T. buccalis	67	179	133
T. parva	96	196	163

DISCUSSION

The pentavalent arsenicals, being less oxidizable than the trivalent series of products, and therefore more stable, are especially suitable for clinical use of surface infections and for oral administration.

In a personal communication, Raiziss[6] states that aldarsone (sodium-methylene-sulfonamino-hydroxy-phenyl-arsonate) and acetarsone (2-acetyl-amino-4-hydroxy-phenyl-arsonic acid) from their structural formulas are somewhat closer related to arsphenamine than carbarsone (p-carbamino-phenyl-arsonic acid). In addition to the arsonic acid group, carbarsone has a carboxylic acid group which is considered to be less therapeutic than the hydroxyl and amino groups which aldarsone and acetarsone have in common. In acetarsone the acetyl group is more firmly bound to the amino group than in the case of aldarsone in which the combination of the amino group with the methylene sulfonic acid group is firm.

Attempts to determine the direct killing power of the drugs for trichomonas by bringing relatively high concentrations of the drugs into contact with the organisms are not altogether satisfactory because of the insolubility of two of the preparations, acetarsone and carbarsone. Aldarsone, which is very soluble, was found by Bland and Rakoff[5] to destroy *Trichomonas vaginalis* in less than five minutes in a concentration of 1:30 and almost at once in a concentration of 1:10. Saturated solutions of a heavy suspension of acetarsone had little effect upon the organisms after a period of observation of one hour. Subsequent experiments have shown that suspensions of carbarsone also have little immediate effect upon the flagellates. Carbonated solutions of acetarsone 1:20 did not inactivate the organisms after one hour. More concentrated solutions of acetarsone and carbarsone require the addition of sodium carbonate in sufficient concentration to destroy the organisms by osmotic pressure effects alone.

Hegner and Eskridge[1] studied the effect of dilute carbonated solutions of carbarsone on cultures of *Trichomonas hominis*. They found that concentrations of 0.1 and 0.2 per cent killed the organisms within 4 days but not within two days, while concentrations of 0.3 and 0.5 per cent destroyed the organisms within two days. These results were confirmed by Gabaldon[2] who noted that carbarsone diluted in the culture fluid at a concentration of 0.3 per cent was lethal for *Trichomonas hominis* and a rat trichomonad, probably *T. para*, in less than seventy-two hours. In 0.05 per cent solutions death of all the organisms rarely occurred after an exposure of five days.

While studying the action of carbarsone on the cycle of development of *T. hominis* in culture, Gabaldon noted that in a concentration of 0.05 per cent an increase in the trichomonad population occurred in the first twenty-four hours, in 0.1 per cent solutions an increase rarely occurred, and in greater concentrations increases were never observed.

A comparison of these results with our observations confirms our belief that although the concentrations which we have designated as trichomonadostatic values are not sufficient to sterilize a healthy culture of the organisms in forty-eight or seventy-two hours, they will prevent the multiplication of the flagellates. The destruction of the organisms in the inoculum probably results from a number of factors in addition to the sub-lethal action of the drug, namely the inability of the organisms

to survive long without multiplication, their inability to produce resistant stages such as cysts, the action of bacteria upon the flagellates and the culture media.

The trichomonadostatic value has a definite practical significance in addition to affording an adequate means of comparison of the effect in vitro of the several drugs upon trichomonas. The most troublesome factor in attaining a permanent cure in the treatment of protozoan infestations is the prevention of recurrences after nearly all the organisms have been destroyed. In patients with trichomonas vaginitis, the eradication of all but a few of the organisms by mechanical means or by chemotherapy is easy of attainment; to destroy the few survivors which rapidly reinfest the vagina is frequently an annoying therapeutic problem. Indeed, the effectiveness of the dry form of treatment of trichomonas vaginitis with antiseptic powders is largely the result of the maintenance over a considerable period of time of a trichomonadostatic environment.

The comparative effective concentrations of the drugs with relation to their comparative toxicity merit consideration in view of the serious toxic effects which may result from absorption of large dosages. Although in the treatment of trichomonas vaginitis the pentavalent arsenicals are widely used by vaginal insufflation and in suppository form, more recently they also have been given by mouth. In the elimination of several intestinal protozoan infestations their administration per os is the rule.

Gabaldon[7] found that 150 mg. per kilogram of body weight was the minimal effective dose of carbarsone when given by mouth to infested rats each day for five consecutive days. It was found that this yielded a percentage concentration of carbarsone in the large intestines estimated to be 0.47. A carbarsone concentration of 0.3 per cent killed rat trichomonads within twenty-four to forty-eight hours in vitro, supporting the belief that, in rats, carbarsone acts upon trichomonads directly, as it appears to do in cultures.

It is questionable whether a concentration of 0.3 per cent carbarsone can be reached in the intestine of human beings with the dosages recommended for oral use even when used over a prolonged period of time.

The marked increase in the toxicity of carbarsone following the addition of sodium carbonate to increase its solubility, as found during the course of this study, is noteworthy. The increase in toxicity is apparently proportionate to the concentration of carbonate. The clinical importance of this observation, especially when the drug is taken internally is apparent. The effect of sodium carbonate upon the pentavalent arsenicals, especially the insoluble members, acetarsone and carbarsone, requires further investigation.

In a recent study Armaghan[8] has shown that in rats infected with Giardia a dose of 0.75 gm. of aldarsone per kg. of body weight, which is less than one-tenth the maximum tolerated dose, seemed adequate to effect a cure in most animals.

NOTE: Chemotherapeutic data including the toxicity of a number of pentavalent arsenicals and their effect upon trichomonads in vitro and in vivo have appeared in a study by Nelson and Tatum (J. Pharmacol. & Exper. Therap. 63: 122, 1938). Among 10 pentavalent arsenicals tested were acetarsone, carbarsone, tryparsamide

and mapharsen. These workers also noted a higher therapeutic index for carbarsone than for acetarsone, while tryparsamide was apparently the most effective. So far as we know, aldarsone was not included in their study.

Armaghan and Mediary (Am. J. Hyg. 27: 250, 1938) have recently published data indicating that aldarsone is of value in the treatment of infestations with a number of intestinal protozoa in man, including *T. hominis.*

The pentavalent arsenicals when administered per os to white rats are not highly toxic, being tolerated in doses of 2 gm. per kilo or more. In other laboratory animals, however, these drugs are not tolerated nearly so well.

In view of these findings the considerably lower toxicity of aldarsone, when tested on white rats, indicates that it is to be preferred to acetarsone or carbarsone for the treatment of protozoan infestations. In the treatment of trichomoniasis it has the further advantage of a higher trichomonadicidal value when tested in vitro.

It may be concluded that the chemotherapeutic index of aldarsone in the treatment of trichomonas infestations is several times greater than that of acetarsone or carbarsone by virtue of its more effective action against the parasite and its lower toxicity for the host.

SUMMARY

1. A comparison of the chemotherapeutic efficacy of aldarsone, acetarsone, and carbarsone in the treatment of trichomonas infestations was made, based upon their relative inhibiting effects upon trichomonads in vitro and their relative toxicity for rats.

2. The toxicity of the drugs was based on the maximum tolerated dose per kilogram when given to rats per os.

Aldarsone was tolerated better than the other compounds, the maximum tolerated dose being in excess of 6 gm. per kilogram of body weight, while only one of six animals succumbed to 8 gm. per kilogram.

3. The maximum tolerated dose of acetarsone soluble was more than 3 but less than 4 gm. per kilogram of body weight.

4. The toxicity of carbarsone varied with the amount of carbonate used in preparing the solution. Thus with 0.5 gm. of carbonate per gram of carbarsone 4 of 5 rats tolerated 5 gm. per kilogram of body weight; with equal parts of each 5 gm. were not tolerated by any of 5 rats, while 4 gm. were tolerated by 3 of 4 rats; when the carbonate was added in excess only 2 gm. per kilogram were tolerated.

5. The inhibiting or trichomonadostatic values were determined by finding the lowest concentration of drug in culture media which prevented the growth of the flagellates; these included *Trichomonas vaginalis, T. hominis,* and *T. buccalis* from the vagina, bowel, and mouth of human beings, respectively, and a cultivable trichomonad from the feces of a white rat, *T. parva.*

6. The average trichomonadostatic concentrations of aldarsone ranged from about one-third to one-half that for acetarsone and carbarsone. Carbarsone was slightly more effective than acetarsone.

7. *Trichomonas vaginalis* was considerably more susceptible to the pentavalent arsenicals than were the other species; the inhibiting con-

centration of aldarsone was 45 mg. per cent (1:2220), of acetarsone 96 mg. per cent (1:1040), of carbarsone 75 mg. per cent (1:1330).

Trichomonas hominis, T. buccalis, and *T. parva* showed greater resistance to the arsenicals in the order named.

8. It is concluded that of the three pentavalent arsenicals, aldarsone has by far the highest chemotherapeutic index in the treatment of trichomonas infestations, while carbarsone is somewhat more effective than acetarsone.

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TREATMENT OF PELVIC INFLAMMATION BY THE IONTOPHORESIS OF A CHOLINE COMPOUND*

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IN A previous communication, the underlying principles upon which the treatment of pelvic inflammatory conditions by iontophoresis is based, together with the technique and the results obtained in 10 patients, were described.[1]

This report reviews the treatment of 50 patients by the same method.

The original technique has been changed so that at the present time 20 c.c. of a 0.5 per cent solution of acetyl-beta-methycholine-chloride† is used instead of a 1 per cent solution. The vaginal electrode has also been modified, so that it now consists of a thin cylindrical shaft, 3/8 of an inch in diameter and 8 inches long, to one end of which is attached by a central pivot a thin bar 2 inches long and 3/8 of an inch wide. The proximal end of the shaft has a terminal for the attachment of the conducting cord.

Gauze, saturated with a 0.5 per cent solution of acetyl-beta-methylcholine-chloride, is placed over the bar on the distal end of the electrode and then introduced into one side of the posterior vaginal fornix. Pressure on the other end of the electrode swings the bar across the vaginal fornix. The ends of the gauze are then firmly tucked into the vaginal fornices around the bar of the electrode. The speculum is withdrawn and the positive pole of the galvanic current attached to the vaginal electrode. The negative pole is attached to a well-moistened felt pad, 6 inches square, which is placed on the lower abdomen. Fifteen milliamperes of current are applied for twenty minutes.

Of the 50 patients treated, 11 were operated upon after treatment, 4 were treated after a preceding operation for other conditions, and the remaining 35 received treatment only and were at no time subjected to any operative procedure.

The average age of these patients was 29 years, the youngest being 19 years old and the oldest 46. Forty-five women were married and five were single. The

*Read at the Academy of Medicine, Section of Obstetrics and Gynecology, January 25, 1938.

†The acetyl-beta-methylcholine-chloride (mecholyl) was supplied by Merck & Co., Inc.

chief symptoms presented by this group of patients were pain in the lower abdomen, in one or the other quadrants, and back. Thirty-three had urinary frequency, 36 cervical discharge, and 9 dysmenorrhea and some menstrual irregularity. Seven had fever of 101° F. or over, prior to the institution of treatment.

In this series of patients, those having any pelvic mass or thickening, whether due to inflammation with or without additional pathology, or whether noninflammatory, were treated, in an attempt to determine the limitations of the modality. The diagnoses, the number of treatments given, the time of treatment, and the results obtained are shown in Table I.

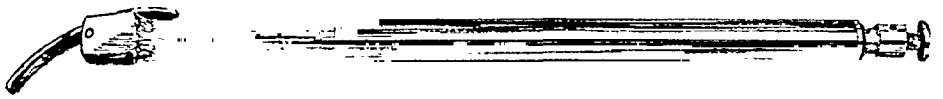


Fig. 1.—Position of movable bar for introduction into the vaginal fornix.



Fig. 2.—Position of movable bar after introduction.

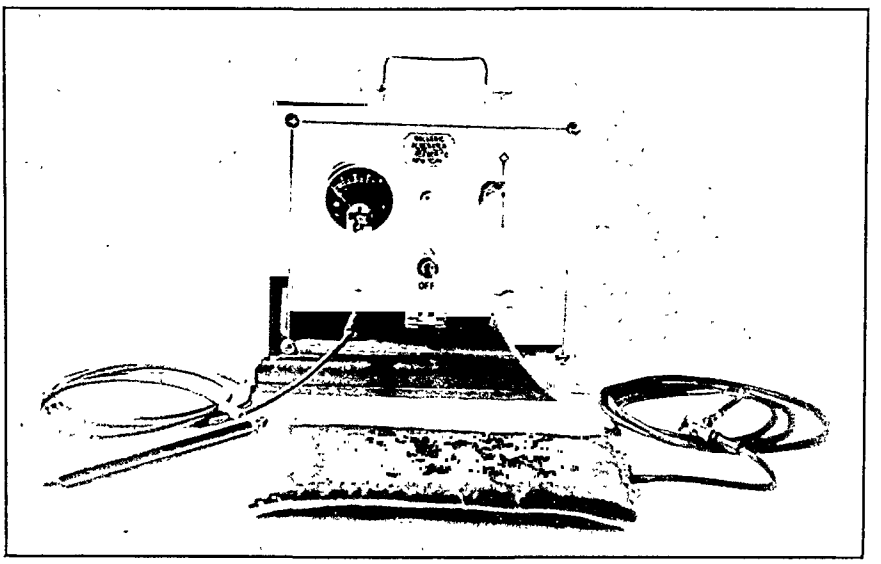


Fig. 3.—Outfit required for iontophoresis.

In 11 patients who were subjected to operation after treatment with iontophoresis, eight had an association of salpingo-oophoritis with other pathological conditions. At operation it was found that the inflammatory exudate had subsided, but that the additional pathology, as shown in Table II, remained unaltered and appropriate operative treatment was therefore instituted. In three other patients, iontophoresis was given for variable lengths of time to determine the nature of the existing masses. No beneficial results were obtained by the treatment, and at operation the pathologic conditions indicated in Table II were found.

TABLE I. NONOPERATED

	NO. OF CASES	NO. OF TREATMENTS			TIME (IN DAYS)			RESULT				REMARKS
		LEAST	MOST	AVERAGE	EARLIEST	LATEST	AVERAGE	CURED	RELIEF	NO CHANGE	RECURRENCE	
Pelvic Inflammation												
Salpingo-oophoritis	20	3	19	7	5	32	20	17	1	2	3	Exudate completely disappeared in cases cured
Salpingo-oophoritis, ovarian cyst	3	4	20	10	30	65	48	--	3	--	--	Exudate disappeared; cyst, no effect
Salpingo-oophoritis, retroversion, Nabothian cyst	4	1	12	7	2	60	43	--	4	--	--	Exudate disappeared; Nabothian cyst and retroversion, no effect
Salpingo-oophoritis, cervicitis, Nabothian cyst	3	7	9	8	16	39	26	--	3	--	--	Exudate disappeared; Nabothian cyst, no effect
Salpingo-oophoritis, Nabothian cyst, Bartholin abscess	1	6	--	6	22	--	22	--	1	--	--	Exudate disappeared; abscess opened
Salpingo-oophoritis, Nabothian cyst, gonorrhea, ovarian cyst	1	9	--	9	18	--	18	--	1	--	--	Exudate disappeared; ovarian cyst, no effect
No Pelvic Inflammation												
Fibroid, cervicitis, Nabothian cyst	1	7	--	7	31	--	31	--	--	1	--	Mass and cysts unchanged
Pregnancy, gonorrhea	1	14	--	14	46	--	46	--	--	1	--	No effect on gonorrhea or pregnancy
Retroversion, prolapsed ovary	1	27	--	27	120	--	120	--	--	1	--	No effect
Pelvic hematoma, following preceding operation	4	12	28	19	40	240	122	--	--	4	--	Slight diminution in size only

TABLE II. OPERATED

	NO. OF CASES	NO. OF TREATMENTS			TIME (IN DAYS)			RESULT				REMARKS
		LEAST	MOST	AVERAGE	EARLIEST	LATEST	AVERAGE	CURED	RELIEF	NO CHANGE	RECURRENCE	
Pelvic Inflammation												
Salpingo-oophoritis, plus other pathology associated with: Ovarian cysts 3, Fibroid 1, Retroversion 1, Abscess 1, Prolapsed ovary 1, Hydrosalpinx 1	8	2	20	9	4	98	42	--	8	--	--	Exudate gone; coexisting pathology, unchanged
No Pelvic Inflammation												
Carcinoma of ovary and sigmoid	1	8	--	8	19	--	19	--	--	1	--	Differential diagnosis
Fibroid, ovarian cyst	1	4	--	4	9	--	9	--	--	1	--	Differential diagnosis
Ovarian cyst	1	12	--	12	150	--	150	--	--	1	--	Differential diagnosis

TABLE III

	NO. OF CASES	NO. OF TREATMENTS			TIME (IN DAYS)			RESULT			
		LEAST	MOST	AVERAGE	EARLIEST	LATEST	AVERAGE	CURED	RELIEF	NO CHANGE	RECURRENCE
Pelvic Inflammation											
Nonoperated	32	1	20	7.4	2	65	26.1	17	13	2	3
Operated	8	2	20	9.0	4	98	42.0	--	8	--	--
No Pelvic Inflammation											
Nonoperated	7	7	28	17.7	31	240	97.8	--	--	7	--
Operated	3	4	--	8.0	9	--	59.3	--	--	3	--

DISCUSSION AND SUMMARY

It has been repeatedly demonstrated that hyperemia is an important factor in the treatment and elimination of inflammation. In the pelvis, hyperemia may be induced by various measures, such as douches, the vaginal hot water bag (Elliott), external heat, diathermy and short wave currents. It has been demonstrated that acetyl-beta-methylcholine-chloride introduced by iontophoresis initiates a hyperemia of from four to eight hours' duration, and this action was relied upon to effect a definite result in cases of pelvic inflammation. My experience with this therapeutic method has verified the correctness of these premises (Table III).

Of the 50 patients treated, 40 had varying degrees of inflammation of one or both adnexa, with or without additional pathology. Twenty of these 40 cases had adnexal inflammation only. In 17 of these 20, complete remission of the inflammation occurred with a disappearance of symptoms and an apparent restitution of the structures to normal. In the other 20, in every instance the inflammatory exudate disappeared, but the associated pathologic conditions remained unaffected. In 8 of the group with associated pathology, we were able to demonstrate at a subsequent operation the existence of the residual pathology. In the group of 10 cases in which there was no satisfactory result after adequate periods of treatment, 3 patients were operated upon, and in these the masses were found to be noninflammatory. The diagnosis in the 7 not operated upon, is shown in Table I.

CONCLUSION

From the foregoing, it is evident that whenever the pelvic pathology consists of an exudative inflammatory process, a prompt recession and restoration to normal occurs following treatment by iontophoresis of acetyl-beta-methylcholine-chloride. On the other hand, if the pathology includes organized inflammatory products or definite pathologic tissue alteration, such as cysts, or tumors, no change is produced.

It is reasonable, therefore, to conclude that in the method of treatment by iontophoresis of acetyl-beta-methylcholine-chloride, we have a therapeutic means of differential diagnosis of pelvic masses, as well as an efficient modality for the rapid cure of pelvic exudative inflammation in any stage.

REFERENCE

(1) *Jacoby, A.:* Am. J. Obst. & Gynec. 31: 93, 1936.

151 West Seventy-Seventh Street

Hammar, S.: Theca Cell Tumors, Acta obst. et gynec. Scandinav. 17: 516, 1937.

Hammar found reports of 18 theca cell tumors in the literature and adds a case of his own. His patient was 20 years old and in her the tumor produced an amenorrhea.

J. P. Greenhill.

A COMPARATIVE STUDY OF THE EFFECTIVENESS OF TWO ANTISEPTICS IN PREVENTING INFECTION FOLLOWING DELIVERY

With a Report on 1,000 Cases

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THIS report is contributed in the interest of aiding in the evaluation of a new antiseptic by comparing it with one which is accepted for obstetric use. The new antiseptic, a soluble concentrate of synthetic alkyl and halogen phenol derivatives* was compared with mercurochrome (dibromo-oxymercuri-fluorescein-sodium).

Some information as to the antiseptic and germicidal potency of the new product may be gained from Table I of minimum germicidal concentrations destructive for a number of common pathogenic microorganisms according to experiments conducted in the manufacturers' laboratories.

Table I

Microorganism	Temperature	Minimum germicidal concentrations in 10 min.
Staph. aureus	20° C.	1:300
Staph. aureus	37° C.	1:700
Strept. (Hemolytic)	37° C.	1:750
Strept. viridans	37° C.	1:1400
B. coli	20° C.	1:900
B. typhosus	20° C.	1:1000
B. pyocyaneous	37° C.	1:350

Among other things, this table indicates the antiseptic effect of "amphyl" upon pyogenic cocci, which play a role in both ante- and post-partum complications, and shows that these microorganisms are killed by comparatively low concentrations.

A total of 1,000 cases were studied; in 500 cases mercurochrome was utilized, and in the other 500 cases amphyl was used. Mercurochrome was used according to the technique suggested by Mayes, and amphyl was used as a 5 per cent tinted aqueous solution for external painting, and as a 2 per cent aqueous solution for vaginal instillation.

The technique was as follows:

1. The external genitals were shaved and scrubbed with tincture of green soap.

2. The external genitals and adjacent area of the thighs and abdomen were painted or sprayed with a De Vilbis atomizer, using a tinted solution of 5 per cent amphyl in the one group and an aqueous-alcohol-acetone solution of mercurochrome in the other.

3. Utilizing the syringe suggested by Mayes, 3 drams of the aqueous 2 per cent solution of amphyl in the one group, and of a 4 per cent mercurochrome solution in

*Amphyl furnished through the courtesy of the Lehn & Fink Products Corporation.

the other, were injected into the vagina. The injection was made at a depth of from 4 to 5 inches; the point of the syringe was kept close to the vaginal floor and the barrel close to the pubis. The labia were held firmly together around the syringe while the contents were being injected, in order to distend the vagina with the solution and to prevent loss of the solution, as much as possible.

The routine up to this point was followed in each case upon admission.

4. The instillation of mercurochrome and amphyl and external painting were repeated every twelve hours during labor, and prior to all vaginal examinations done during labor.

5. Before draping in the delivery room, the parts were cleansed and then sprayed or painted with the aqueous-alcohol-acetone solution of mercurochrome or with the tinted 5 per cent solution of amphyl. The perineum was then depressed and 2 drams of the solution were put into the vagina.

6. At the conclusion of the delivery, a solution of 2 per cent amphyl or a 4 per cent solution of mercurochrome, in water was instilled into the vagina.

7. These solutions were also instilled into lacerations and episiotomy wounds before repair.

The standard of morbidity utilized in this discussion is identical with that used by Mayes, viz., "a rise in temperature to 100.4° F. on two consecutive days, not including the first twenty-four hours, and occurring on or before the tenth day." These temperatures are taken by mouth every four hours.

The distribution of cases in each group was as follows:

Amphyl group of primiparas	173 cases
Amphyl group of multiparas	327 cases
Mercurochrome group of primiparas	183 cases
Mercurochrome group of multiparas	317 cases

The average age of the patients in both series showed very little variation. Amphyl group of primiparas average 22.03 years and mercurochrome group of primiparas 22.11 years. Amphyl group of multiparas averaged 23.8 years and mercurochrome group of multiparas, 22.72 years.

The number of internal examinations done, also ran rather closely parallel. In rectal examinations there were 3.34 per patient in amphyl group of primiparas, and 3.33 in mercurochrome group of primiparas. There were 3.24 per patient in amphyl group of multiparas and 2.45 in mercurochrome group of multiparas.

In vaginal examinations, there were 0.092 per patient in amphyl group of primiparas, and 0.18 in mercurochrome group of primiparas; 0.079 in amphyl group of multiparas and 0.07 in mercurochrome group of multiparas.

Table II indicates the average time elapsing between the rupture of membranes to the delivery, the average length of time from the last instillation of antiseptic solution to delivery, the average duration of labor, and the average number of instillations.

These figures do not show any striking differences and are little more than of academic interest.

Table III is a tabulation of the spontaneous and operative incidence in the deliveries.

TABLE II

	AMPHYL		MERCUROCHROME	
	PRIM.	MULT.	PRIM.	MULT.
Time from rupture of membranes to delivery	4.46 hr.	3.04 hr.	5.61 hr.	4.32 hr.
Time from last instillation to delivery	7.51 hr.	6.59 hr.	8.43 hr.	5.77 hr.
Duration of labor	14.85 hr.	10.14 hr.	15.98 hr.	11.33 hr.
Number of instillations per patient	1.20	1.09	1.28	1.10

TABLE III

TYPE OF DELIVERY	AMPHYL		MERCUROCHROME	
	PRIM.	MULT.	PRIM.	MULT.
Spontaneous	149 (86.2%)	305 (93.3%)	134 (73.4%)	301 (95.0%)
Low forceps	18 (10.3%)	5 (1.5%)	27 (14.7%)	2 (0.6%)
Midforceps	1 (0.6%)	2 (0.6%)	6 (3.3%)	2 (0.6%)
High forceps	0	1 (0.3%)	0	0
Breech extraction	3 (1.7%)	10 (3.1%)	11 (5.9%)	8 (2.5%)
Cesarean section	1 (0.6%)	3 (0.9%)	5 (2.7%)	1 (0.3%)
Vaginal cesarean section	0	0	0	1 (0.3%)
Version	1 (0.6%)	1 (0.3%)	0	2 (0.6%)

From Table III it appears that there was slightly more operative procedure in the mercurochrome group than in the amphyl group.

Table IV shows incidence of perineal injury.

TABLE IV

	AMPHYL		MERCUROCHROME	
	PRIM.	MULT.	PRIM.	MULT.
Episiotomy	52 (29.9%)	2 (0.6%)	78 (40.8%)	2 (0.6%)
1° Laceration	28 (16.1%)	52 (15.8%)	42 (22.8%)	52 (16.3%)
2° Laceration	17 (9.8%)	20 (6.1%)	13 (7.1%)	16 (5.0%)
3° Laceration	0	0	0	1 (0.3%)

The gross and net morbidity are indicated in Table V.

It is evident from Table V that the difference between the groups is practically negligible. In the amphyl group of 500 cases there were 31 morbid cases of presumably birth canal origin or an incidence of 6.2 per cent, while in the mercurochrome group, there were 32 morbid cases, an incidence of 6.4 per cent. Also it is shown here that the infection incidence in primiparas is 9.2 per cent and in multiparas 4.6 per cent.

TABLE V

	AMPHYL		MERCUROCHROME	
	PRIM.	MULT.	PRIM.	MULT.
Gross	20 cases	22 cases	20 cases	20 cases
Eliminated (not birth canal injections)	4 cases	7 cases	3 cases	5 cases
Net	16 cases (9.25%)	15 cases (4.5%)	17 cases (9.29%)	15 cases (4.7%)

The cases eliminated from the gross morbidity were only those in which an extra birth canal origin could definitely be ascertained, and below are indicated the numbers of cases and causes of morbidity in the exempted cases.

AMPHYL

Primiparas (4 cases):

1. Influenzal pneumonia (present on admission)
2. Osteoperiostitis, internal tuberosity right knee (present on admission)
3. Upper respiratory infection (present on admission)
4. Temperature before delivery, unknown origin, profound secondary anemia

Multiparas (7 cases):

1. Abscess of face (secondary to tooth infection)
2. Acute mastitis
3. Cellulitis of the thigh
4. Pyelitis
5. Pericarditis with effusion
6. Upper respiratory infection with bronchitis
7. Acute enteritis

MERCUROCHROME

Primiparas (3 cases):

1, 2, 3. Acute mastitis

Multiparas (5 cases):

1. Pyelitis
2. Acute pulmonary tuberculosis
3. Dental abscess
4, 5. Acute mastitis

The duration of morbidity in each group is designated in Table VI.

TABLE VI

DAYS	AMPHYL		MERCUROCHROME	
	PRIM.	MULT.	PRIM.	MULT.
2	1	2	1	6
3	6	8	2	5
4	3	1	3	2
5	2	0	4	1
6	3	0	1	0
7	0	0	2	1
8	0	1	1	0
9	0	1	0	0
10	0	1	0	0
11	1 (died)	0	1	0
12	0	0	0	0
13	0	0	0	0
14	0	0	1	
15	0	0	0	
16		1	1	
Totals	16	15	17	15

The average length of morbidity in each series was as follows: Amphyl group of primiparas 3.85 days, multiparas 4.93 days. Mercurochrome group of primiparas 6.66 days, and multiparas 3.12 days.

The morbidity in amphyl group of primiparas includes the death which occurred on the eleventh day and has been included as an eleven day morbidity.

In the entire series of 1,000 cases, the number of spontaneous and operative deliveries are shown in Table VII, also the incidence of infection in each.

TABLE VII

TYPE OF DELIVERY	CASES	INFECTION	PERCENTAGE	
Spontaneous	889	48	5.4%	
Low forceps	52	6	11.5%	
Midforceps	11	1	9.0%	
High forceps	1	0	0	7.4%
Breech extraction	32	1	3.1%	
Abdominal cesarean section	10	7	70.0%	
Vaginal cesarean section	1	0	0	
Version (podalic)	4	0	0	
Totals	1000	63	6.3%	

CONCLUSIONS

1. It is evident from the preceding that the amphyl and mercurochrome techniques are about of equal efficiency in the prevention of puerperal infection.

2. The incidence of infection was definitely less in spontaneous deliveries (5.4 per cent) than operative deliveries (7.4 per cent), and twice as great in primiparas as in multiparas and at least part of this is undoubtedly due to the greater incidence of operative deliveries in primiparas (9.2 per cent), than in multiparas (4.6 per cent).

3. Under conditions where economy is important, amphyl, being less expensive, might be preferable.

REFERENCE

Mayes, H. W.: AM. J. OBST. & GYNEC. 30: 80, 1935.

1000 PARK AVENUE

Foederl, Viktor: Pathology and Clinical Course of Disgerminoma Ovarii, Arch. f. Gynäk. 165: 392, 1938.

From a study of 13 cases of disgerminoma ovarii in the Vienna Frauenklinik, the author concluded that the malignant character of this tumor cannot be questioned. These newgrowths are malignant microscopically, have marked powers of invasion and produce metastases into other pelvic structures and through the lymphatics into the retroperitoneal spaces, early and rapidly. Careful microscopic studies showed downgrowth through the basal membrane in almost every instance. In addition, tumor cells could be found in the lymphatics and the blood vessels of the hilus. The tumor capsules also showed perforation by the tumor cells. Foederl believes that both granulosa cell tumors and disgerminoma arise from indifferent mesenchymal cells.

RALPH A. REIS.

THE USE OF BLOOD TRANSFUSIONS IN THE TREATMENT OF PYELITIS COMPLICATING PREGNANCY

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THE frequency of pyelitis complicating pregnancy is usually greatly underestimated, there being several reasons for this. Many of the attacks are mild and have a tendency to subside spontaneously, so that they are either not reported or are undiagnosed. Only the individuals with more severe cases are admitted to the hospitals and even in reports from these institutions are found discrepancies.

For example, Traut said that pyelitis occurred twice in each 100 pregnant women at the New York Hospital and the expectancy for obtaining a nonviable infant from women suffering from this condition is 3 times as great as in normal pregnancy, while abortions, premature labors and full-term stillbirths are common. Their fetal mortality was 10 per cent, as compared to their clinic fetal mortality of 3.3 per cent. Mussey found evidence of some degree of pyelitis in 20 per cent of all pregnant women. DeLee says that two-thirds of all women dying during pregnancy have had pyelitis at some time, while Baird found signs of infection in 42.5 per cent in 1,000 cases studied and Emge reported an incidence of 7 per cent.

The treatment of a condition occurring with such frequency and followed by the well-known and serious sequelae should command attention. The fact that many are concerned with this problem is well illustrated by the voluminous literature which has collected in recent years, and the several new methods of treatment which have been advocated. It is the purpose of this short paper to call attention to what must be a well-known but hitherto unmentioned adjunct in treatment; i.e., blood transfusions.

It has been our experience at the Baltimore City Hospitals and the University Hospital, Baltimore, that the patient who has a resistant form of pyelitis almost always has a very definite anemia, this anemia becoming more severe as the condition advances. It is our opinion that the disease is either an etiologic or a decidedly aggravating factor in this anemia and that the anemia itself so lessens the resistance of the patient to infection that little improvement from the pyelitis can be expected until it is overcome. Therefore, in addition to the recognized and accepted forms of treatment, we have added in recent years the practice of carefully watching for anemia, and, when found, of giving blood transfusions. The amount of blood at any one transfusion is usually small, 150 c.c. to 250 c.c., but they are repeated at intervals of a few days until the patient shows definite evidence of improvement.

Should it be decided to treat the patient with sulfanilamide, transfusions become even more necessary, and it should be the rule that the treatment should not be begun until the patient's red blood count and

hemoglobin have been brought to a safe level. Also as the treatment continues there should be daily determinations and an available donor should always be held in readiness.

With this addition to our therapy, we have found (1) a 30 per cent reduction in hospitalization, (2) a much lessened instance of ureteral catheterization and drainage, and (3) an entire absence of the necessity for therapeutic abortion.

The following are a few case histories which illustrate the beneficial effects of even one or two small blood transfusions:

CASE 1.—M. T., a 22-year-old primigravida, was admitted to the University Hospital Aug. 26, 1937. Her past and family histories were noncontributory, and her prenatal course was apparently normal until August 20, one week before admission, when she noticed some frequency of urination with burning, pain in the right kidney region and fever and chills. On August 23 her temperature reached 104° F. and the urine contained numerous pus cells. She was treated at home with forced fluids, alkalinization of the urine, postural drainage, and bed rest. Patient improved slightly under this, but her tenderness, fever, and pyuria persisted, and she was hospitalized. On admission her temperature was 100.6° F. and her urine contained a few white blood cells with clumping. The blood chemistry was normal and the blood culture negative. The urine culture was positive for colon bacillus. The blood count on admission revealed a moderate secondary anemia with a red blood count of 3,890,000 and a hemoglobin of 74 per cent. Alkalinization and postural drainage were continued and the patient was given a blood transfusion of 300 c.c. of citrated blood. On the day of admission her temperature reached a maximum of 102° F., following which it subsided to normal on the third day and remained normal thereafter. Subsequent urinalyses revealed many clumped white blood cells, and the patient lost all of her subjective symptoms. She was discharged in good condition, the urine at this time showing no pus cells and the urine culture being negative.

In this case it would appear that the course of the disease was decidedly shortened and that treatment was held to a minimum of simple, safe procedures.

CASE 2.—E. H. This patient, a 16-year-old secundigravida, was admitted to the University Hospital Apr. 12, 1937, from the Out-Patient Department in the thirtieth week of her pregnancy because of pyelitis and anemia. Her past and family histories were noncontributory and her previous pregnancy and labor had been normal and uneventful. She was first seen in the prenatal clinic July 14, at which time she seemed normal and remained so until August 1, when she developed pain in the left lumbar region. This pain was accentuated on urination, and at the same time she noticed that her urine had become very cloudy. When the urine was examined many pus cells were found. Therefore she was treated on the Outside Service with alkaline therapy and forced fluids. Under this regime she became comfortable but the urine continued to contain many pus cells in clumps and the blood count showed only 2,620,000 red blood cells and a hemoglobin of 48 per cent. Because of these findings she was admitted to the hospital for further treatment of the pyelitis as well as treatment of the anemia. At the time of admission her urine contained many pus cells. Urine culture was positive for *B. coli*, and the blood culture was negative. She was placed on the regime of forced fluids, urine alkalinization, and antianemia diet. After several days she showed no improvement and was given two transfusions on alternate days consisting of 400 c.c. of whole citrated blood each time. On August 28 her red blood count had increased to 3,480,000 with a hemoglobin of 78 per cent; urine contained no pus cells and temperature was normal. At the time of discharge on August 30, she was in good condition. The urine culture taken on that day showed no growth after five days. The patient went through the remainder of her pregnancy without any further attacks and six months later was clinically well.

In this case the subsidence of the subjective symptoms was not accompanied by clinical evidences of improvement, and it was only after blood transfusions that the urine became negative. It may be assumed that in this case the patient was saved a latent or chronic type of infection. The case was unusual also in that the symptoms were referable first and last to the left urinary tract alone.

CASE 3.—M. M. This patient, a 22-year-old primigravida, was admitted to the hospital May 10, 1937. This was her second admission, the first having been just a few days before and for the same reason, that is, pyelitis complicating a pregnancy of twenty-five weeks' duration. The patient was quite uncomfortable when she entered the hospital, her temperature was fluctuating between 103° F. and subnormal, and the urine contained a fair number of pus cells with clumping. On admission the blood chemistry was normal, blood culture negative, but the urine culture positive for *B. coli*. She was placed on routine treatment but showed little or no improvement, and on May 27 she was given 300 c.c. of whole citrated blood. This was followed on June 1 by a second transfusion of 350 c.c. after which her condition immediately improved, and on June 4 she was allowed out of bed and on June 6 she was discharged. At full term she was readmitted to the hospital and delivered of a normal living child. At this time there were no signs or symptoms of pyelitis present.

SUMMARY AND CONCLUSIONS

1. Pyelitis is a very frequent complication of pregnancy, probably occurring in varying degrees of severity in about 25 per cent of all pregnant women.

2. The condition frequently is quite resistant to the ordinary methods of treatment.

3. In many cases if the blood is examined, there is found a definite, and at times severe anemia associated with the pyelitis. The anemia in turn lessens the patient's resistance, and a vicious cycle is thus established, which, unless broken, renders her recovery difficult.

4. A rational and rather safe answer to the problem is found in blood transfusions of fairly small amounts and repeated at intervals until improvement of both the anemia and pyelitis occurs.

5. Transfusions should prove to be especially valuable in those patients treated with sulfanilamide.

6. Three illustrative cases are presented.

Picinelli, G.: On the Therapeutic Value and the Conservability of Placental Blood, Arch. di ostet. e ginec. 2: 83, 1938.

The author points out that the introduction of small transfusions and the increasing variety of their use stimulate new sources of blood. Mentions the use of cadavers' blood as proposed by Judine. The idea which simultaneously developed in Italy and other foreign countries of the utilization of umbilical cord blood for transfusion is practical.

He demonstrates and emphasizes the higher erythropoietic value of placental blood when contrasted to that obtained from the pregnant woman or normal man. He describes the technic of obtaining blood from the umbilical cord and for its preservation, and finds that it may be kept from six to eight days.

A. A. MARCHETTI

BLOOD SUGAR CHANGES IN LABOR AND AFTER DELIVERY

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IT IS a well-known fact that hyperglycemia is common after exercise associated with emotional stress.[1] Rowe and McManus[2] report that low blood sugar levels persist "actually during labor and to within a few minutes of delivery. There is a marked rise in blood sugar on emptying the uterus." Our results do not agree, particularly with respect to labor levels.

The original impetus for this work came from our harrowing experiences with two cases of an atypical form of shock. Shock occurred in each case about an hour after delivery, manifested by a weak and often imperceptible pulse; a blood pressure that dropped to 30 and 40 mm. systolic; cold moist extremities; but a fully conscious, comparatively comfortable patient, without air-hunger or any other complaint. In both cases hemorrhage was ruled out and supportive measures in the form of intravenous glucose in normal saline, and massive doses of suprarenin (in the second case 30 c.c. were used over a period of six hours) were resorted to with the result that both patients snapped out of their "shock" and eventually recovered.

In attempting to find an explanation for their behavior the question of hyperinsulinism came up. Though this could be ruled out on the basis of the lack of response to large quantities of glucose administered intravenously, we found that the literature is notably barren on the subject of blood sugar during pregnancy, labor, and immediately after delivery, and we decided to investigate.

After starting this work a paper by Adair and others[3] entitled "Vascular Collapse in Toxemia of Pregnancy" completely explained one of our cases of "shock," but left us as much in the dark as ever about the other.

Our subjects were selected at random from two of our A. M. prenatal clinics. Blood specimens were taken at each clinic visit, at the same hour, approximately four hours after their respective breakfasts. The average of these figures was taken as each patient's normal. General average proved to be 87 mg. per 100 c.c.

METHOD

After admission to the hospital in labor, a specimen of blood was taken approximately fifteen to thirty minutes before delivery, and another thirty to sixty minutes after the termination of the third stage. For a time fasting sugars were taken on the morning of discharge, but these proved to be so near the predetermined average, that this determination was dispensed with.

From 50 patients originally selected only 25 studies are complete enough to be considered in this report.

There were 6 primiparas and 19 multiparas. Twenty women delivered spontaneously and outlet forceps operations were done on 5. Twelve patients received

only nembutal gr. ivss-vi; 6 had morphine-scopolamine narcosis and an inhalation anesthetic. Seven women required neither analgesia nor anesthesia.

Of the 6 primiparas, all had morphine-scopolamine narcosis; 4 had open-drop ether at the end of the second stage, one gas-oxygen-ether, and the last gas-oxygen. Five of the 6 were delivered with outlet forceps. Their average time in labor was eighteen and one-half hours. The normal blood sugar average in this group was 87.5 mg. The average during labor was 111 mg., a rise of 26.8 per cent. The average in the postdelivery determinations was 115 mg., or a 31.4 per cent rise above average normal.

The 19 multiparas had no inhalation anesthetics; their average duration of labor was eight and one-half hours. Normal average of blood sugar levels was 85.6 mg.; average during labor 107 mg., a 25 per cent rise. Postdelivery average was 119.5 mg., or a 39.8 per cent rise above average normal.

Twelve of these 19 multiparas received pentobarbital sodium, gr. ivss-vi, and the other 7 women required neither analgesia nor anesthesia. In the first group, the normal sugar level averaged 84 mg., the labor average was 100.5 mg., a rise of 19.6 per cent. The postdelivery average level was 118 mg., or 40.5 per cent above the normal average.

Figures for the 7 women who had no medication of any sort show the following; average duration of labor of four hours. An average normal blood sugar of 89 mg.; a labor average of 116 mg., up 30 per cent and a postdelivery average of 128 mg., up 44.9 per cent above normal.

Combining our figures for all the cases, we find our average normal to be 87 mg. Labor average to be 107.6 mg., up 23.7 per cent. Postdelivery average of 120 mg., 38 per cent above normal.

Table I serves to illustrate more graphically the changes noted.

TABLE I

GROUPS	DURATION OF LABOR HR.	AVERAGE NORMAL BLOOD SUGAR	DURING LABOR		POSTDELIVERY	
			BLOOD SUGAR	% RISE	BLOOD SUGAR	% RISE
6 Primiparas (morphine and scopolamine)	18.5	87.5	111.0	26.8	115	31.4
12 Multiparas (nembutal)	10	84.0	100.5	19.6	118	40.5
7 Multiparas (no analgesia)	4	89.0	116.0	30.0	128	44.9
25 Combined	10.5	87.0	107.6	23.7	120	38.0

In only 3 patients, the blood sugar levels, during labor fell below predetermined normal figures. The drop was only 7 mg., or 8 per cent. Postdelivery figures on these 3 were 121 mg., or 40.7 per cent above normal.

In 5 cases after an average rise of 36.4 per cent in blood sugar during labor, there was a fall from 122 to 98 mg., but this last figure was still 9.6 per cent above "average normal."

The highest postdelivery sugar recorded (166 mg.) was by a para ii in labor for thirty-six hours. She delivered spontaneously a 5 pound premature baby and had a retained placenta. One patient had a mild post-partum hemorrhage with no effect on sugar figures.

SUMMARY

Average prenatal fasting sugar level proved to be 87 mg. The average rise during labor was 20.6 mg. or 23.7 per cent above normal. The highest was 151 mg. and the lowest 68 mg. These figures do not agree with those of Rowe and McManus[2] who found no rise until after the second stage. In the hour after delivery there was a further rise of 11.5 per cent above the labor average, to 120 mg., which was 38 per cent above normal.

CONCLUSIONS

There seems to be a fairly consistent rise in blood sugar levels during labor, and a further rise occurs in most cases within the hour after the termination of labor. Hyperglycemic figures were obtained in several patients with no stigmas of diabetes and glycosuria was not seen.

Dangerously low blood sugar levels were not seen either during or after the termination of labor.

It may be of interest to note that neither parity, nor type of delivery, nor use of analgesia or anesthesia seemed to influence the figures obtained.

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NON-EFFECT OF OVARIECTOMY DURING PREGNANCY IN THE RHESUS MONKEY

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THE rôle of the corpus luteum in the production of progestational proliferation of the endometrium, that is, preparation for the nidation of the ovum, is now fully established.[1-6] How soon after nidation, however, the corpus luteum remains indispensable for the maintenance of pregnancy has been determined for only a few mammalian species. The pregnant rat, mouse or rabbit, for example, invariably aborts after castration, while the guinea pig, which has a long span of gestation, can spare its ovaries after the midperiod. In man, the matter is under dispute. From the clinical literature many cases can be cited in which abortion was seen to follow removal of the corpus luteum, while there remain positive cases in which castration did not interfere with pregnancy. Indeed, estrin as well as pregnandiol glucuronidate (degeneration product of progesterone)[7] is recoverable from the urine despite removal of the ovaries. One may infer from this that sooner or later the placenta takes over certain ovarian functions.

It is not the purpose of the present paper to discuss the clinical literature but only to present five experiments on the monkey for whatever of value they may possess toward a solution of the problem.

CONDITIONS IN THE MONKEY

In the monkey implantation occurs at the end of the ninth day following fertilization.[11] The gestation period approximates six lunar months (average 165 days).[8]

Certain events of interest to the present problem have been noted to occur soon after the third week. In the first place, anterior pituitary-like hormone (prolan), present in the urine from the seventeenth day on, disappears after the twenty-first day and does not reappear.[9] Second, about the 25th day the corpus luteum of pregnancy regresses somewhat and assumes a more compact structure,[10] in which

condition it remains for several months. Third, by the end of the fourth week, with the establishment of villi, the destruction by the trophoblast of proliferated uterine epithelium is over.[11] Finally, the female gradually loses all sex responsiveness.[12]

In view of these facts, most of all in view of the establishment of villi by the thirtieth day, one might expect this date to constitute a dead line, before which the corpus luteum is essential, after which it may be removed without disturbance to the implantation. This assumption finds confirmation in the last experiment cited below.

PROTOCOLS

MONKEY 469.—This old multipara weighed 7,870 gm. when she arrived on Aug. 14, 1936; 8,500 gm. later. Her menstrual cycles before conception, which occurred on Jan. 31 and Feb. 1, 1937, day 13 of cycle, were 30, 28, and 27 days in length. The placental sign began on February 18. Palpation from time to time showed a normal pregnancy in progress; the buttocks were maximally colored throughout pregnancy and lactation.[8]

On May 5, *the ninety-fifth day of gestation, the left ovary containing the corpus* luteum of pregnancy was removed. Serial sections of the ovary disclosed the corpus luteum in a good state of preservation.

On July 20, the one hundred seventy-first day of gestation, a normal male baby weighing 360 gm. was born. The mother ate the placenta; her pelvic ligaments were relaxed as normally despite the ovariectomy. The baby nursed well until September 20, when it was used in a crucial experiment.

Summary: Removing one ovary containing the corpus luteum on the ninety-fifth day of gestation, leaving the other ovary intact, in no recognizable manner affected the course of pregnancy, parturition, or lactation.

MONKEY 391.—This 6-kilo female was pregnant when she arrived on April 23, 1935. She gave birth to a 490 *gm. male* baby on June 22, which was removed two days later. On Oct. 17, 1936, the endometrium was excised in the hopes of finding a fourteen-day ovum, but fertilization had not taken place. The next bleeding occurred on November 19; *the placental sign began on December 12. Conception* occurred in the interval despite the contraceptive use of a small rubber sponge soaked in undiluted vinegar. Ovulation was estimated to have occurred on Nov. 28, 1936.

On Feb. 25, 1937, when the fetus was about 89 days old, the left ovary, containing the corpus luteum of pregnancy, was removed. Serial sections showed the corpus luteum to be in exactly the same condition as that of the preceding case (No. 469). On May 13 a 360 gm. male baby was born; the gestation lasted about 166 days, approximately the average for the rhesus monkey. Despite the fact that the mother was not in the best of health, pregnancy seemed perfectly normal. She took little interest in the baby, however, which was removed the next day and raised on a bottle. The mother died on June 7.

Summary: Complete castration on about the eighty-ninth day of gestation caused no abortion despite the poor physical condition of the mother, which delivered a viable baby at term.

MONKEY 457.—Mature female between 4,290 and 4,580 gm. in weight. After a twenty-five- and a twenty-six-day cycle she conceived and on Feb. 7, 1937, the endometrium was enucleated and an eleven-day ovum recovered. The right ovary containing the corpus luteum was also removed. *Conception occurred again on Oct.* 30 and 31, 1937, day 12 of the cycle; the placental bleeding began on November 16. On December 15, the forty-sixth day of gestation, the surviving ovary was removed. Palpation from time to time demonstrated the continuance of a normal pregnancy. By March 5, the one hundred twenty-sixth day of gestation the female had become considerably emaciated, due to tuberculosis as the autopsy later revealed; but the fetus seemed alive and the mother's buttocks red as usual. During the night of March 13 and 14, however, the one hundred thirty-fifth day of gestation, the animal died after first giving birth to a dead male fetus in a good state of preservation. The afterbirth was also delivered.

The hypophysis removed at autopsy showed the usual hypertrophy of pregnancy (at least a fourth larger than normal). There were no changes in this case attributable to lack of pregnancy hormones due to castration, the death of the fetus and of the mother being clearly a consequence of disease.

Summary: Complete castration on the forty-sixth day of gestation did not interrupt pregnancy in this tuberculous female which carried a baby to the one hundred thirty-fifth day and died immediately after delivery.

MONKEY 567.—A mature female weighing 4,710 gm. when she was received on Aug. 3, 1937. Conception ensued consequent upon a single mating on December 6 and 7, days 11 and 12 of the cycle. On Jan. 11, 1938, the thirty-fifth day of pregnancy, the left ovary containing the corpus luteum was removed. Examinations on January 25 and on February 9, indicated a pregnancy going on in normal fashion. On March 5 the uterus and embryo seemed normal but the sex skin several shades paler. On March 11 a bleeding set in and palpation disclosed a soft, mushy uterus. Pregnancy was clearly at an end. The animal was killed on March 14 in an advanced stage of pulmonary and abdominal tuberculosis. The pituitary showed the usual enlargement of pregnancy. The mammary acini were greatly dilated as in a secreting gland. Gestation had lasted but fifty-three days after ovariectomy.

Summary: Semicastration on the thirty-fifth day of pregnancy failed to precipitate abortion, which, however, occurred about fifty-three days later.

MONKEY 466.—A 4,430 gm. female had cycles of 29, 32, and 24 days, respectively, in the fall of 1936. On February 15 she furnished a 1-celled ovum and at this time the left ovary with fresh corpus luteum was removed. In April ovulation followed injection of extract of pregnant mare's serum (Gonadogen Upjohn). On October 25 a thirteen-day ovum was removed by hysterotomy. On December 4 and 5, days 12 and 13 of the menstrual cycle, she conceived again and on December 21 the placental sign appeared. On January 4, the thirty-first day of pregnancy, the surviving (right) ovary was removed. On January 10 the sex skin was several shades paler than normal but returned to a brilliant red after a few days, in which condition it continued. By March the female gave evidence of pulmonary tuberculosis (confirmed at autopsy), but pregnancy continued in perfectly normal fashion. Since a 140-day fetus was desired for a neurologic experiment and since the continuance of pregnancy without ovaries was sufficiently established by this time, the fetus was removed by cesarean section, after which the mother was killed and autopsied. The male fetus was normal as was also every other indicator of normal pregnancy: uterus, placenta, sex color, hypertrophied pituitary.

Summary: This tuberculous monkey despite complete castration on the thirty-first day of gestation, carried a normal, vigorous fetus to the one hundred fortieth day, when it was removed by cesarean section.

DISCUSSION

The results of five experiments, summarized in Table I, clearly show that, at least after the thirty-first day of gestation, the rhesus monkey can dispense with the corpus luteum. This conclusion is justified even though the third and fourth experiments (No. 457 and 567) are thrown

TABLE I. SUMMARY OF CASTRATION EXPERIMENTS

ANIMAL NO.	DAY OF PREGNANCY OPERATED	ONE OVARY OR BOTH REMOVED	RESULT
469	95	One	Normal delivery at term
391	89	Both	Normal delivery at term
457	46	Both	Premature delivery on 135th day; death of mother
567	35	One	Resorption after 88th day
466	31	Both	Normal pregnancy, cesarean section on 140th day

out. This seems hardly necessary, however, for both pregnancies continued two to three months after castration, that is, through the more vulnerable period. The animals achieved this (as did also No. 466) despite general physical debility due to disease.

Abortions are common in the monkey even without surgical interference.[8] Thus, at the time the first two experiments were under way the Carnegie Colony possessed two other females at about the same stage of pregnancy. These were left unoperated, since newborn babies were desired. These two unoperated "controls" aborted, the two castrated individuals went to term!

Except in the case of 567, all females gave ample evidence of endocrine sufficiency, namely in the sex skin of maximal redness; in a full and turgid uterus; in normal, growing mammary glands; in the hypertrophied pituitaries; in the inactive vaginal mucosa,[13] and in the relaxation of pelvic joints.

SUMMARY

A monkey castrated on the thirty-first day of gestation furnished on the one hundred fortieth day a vigorous baby removed by cesarean section. Four additional experiments help to demonstrate the dispensability of the corpus luteum in the monkey after the first month of pregnancy.

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The relation between chronic cervicitis and bladder irritability is emphasized. Frequency of urination of this type is associated with noninfected urine and a normal bladder. The authors believe that it is due to reflex stimulation through the parasympathetic nerves to the bladder. In a high proportion of cases relief is obtained by dilatation and cauterization of the cervix with the electric cautery. In intractable cases, injection of the pericervical nerve plexus, particularly in the region of the bladder base, gives immediate relief without interfering with bladder function. This relief is often transient.

CARL P. HUBER

THE RELATION BETWEEN HYDATID MOLES, RELATIVE ISCHEMIA OF THE GRAVID UTERUS, AND THE PLACENTAL ORIGIN OF ECLAMPSIA*

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ANY working hypothesis applied to the origin of the toxemia syndrome in late pregnancy must be able to correlate in a satisfactory manner the known facts pertaining to the occurrence of eclampsia. The writer wishes to point out very briefly a working hypothesis which has not been discussed before, but which would seem to deserve serious consideration. Attention was first directed to this theory by an inquiry into the relative frequency with which hypertension and albuminuria accompany hydatidiform moles, and for that reason the results of the analysis are presented below.

Individual case reports of eclampsia accompanying hydatid moles have been made from time to time[1, 2] but it has not been known whether such tumors statistically predispose to the development of the toxemia syndrome. During a nine-year period from 1928 to 1937 inclusive, thirty women with hydatid moles were treated at the Los Angeles County Hospital. Ten of these women developed pre-eclamptic toxemia, as evidenced by a sustained blood pressure over 140 systolic and 90 diastolic, the presence of albumin in the urine and the development of the usual subjective symptoms of late toxemia. Three of these ten cases were graded as severe pre-eclampsia, while the remainder were mild toxemias.

Such facts are of greater significance when the duration of the pregnancies is taken into consideration. The cases were arbitrarily divided into early stages (less than four months' amenorrhea, or a tumor below the level of the umbilicus), and late stages (from four to seven months' amenorrhea, or a tumor above the level of the umbilicus). Of the 16 early cases, there were no instances of pre-eclamptic toxemia. All ten of the toxemias were found among the 14 hydatid moles which were of four to seven months' duration, an incidence of 71 per cent. Using the same criteria, it was found that among 3,850 consecutive deliveries at the same hospital there were 346 women (9 per cent) who developed the toxemia syndrome, almost always during the last trimester. In this short series, therefore, the incidence of pre-eclamptic toxemia in women with hydatidiform moles in the middle trimester was almost eight times as high as the incidence of toxemia in late pregnancy.

While such facts are subject to numerous interpretations, it seems reasonable to assume that the more rapid growth of the vesicular

*Received for publication, July 22, 1938.

placenta demands a greater blood supply than does a normal placenta of the same age. To revert for a moment to teleologic reasoning, if the placenta (which appears to be a ruthless parasitic organ existing solely for the maintenance and protection of the fetus, perhaps too often to the disregard of the maternal organism) should be unable to obtain a sufficient maternal circulation for its demands, it might be capable of increasing this supply by raising the systemic blood pressure. Since there are no nervous connections by which the placenta could accomplish this, such a postulate necessitates the concept of a "placental pressor substance" capable of being produced by all chorionic tissue in response to a relative ischemia. Recent contributions[3] in the field of experimental renal hypertension have shown that the kidney is able to effect hypertension by a similar mechanism, and to the same stimulus of reduced blood flow. Since the placenta is the excretory organ of the fetus, it is not illogical to consider that it may also possess a similar secretory function. While the transference of blood from patients with eclampsia to normal pregnant women[4] has not demonstrated any circulating pressor substance, the method does not give conclusive proof of its absence, and furthermore, the same method has yielded negative results in the case of experimental hypertension[5] where a circulating pressor substance must exist.

That the normal placenta is capable of producing pressor substances is indicated by preliminary assays. The rather crude extracts which I have prepared by extracting acetone-desiccated powders of fresh placental mash with Locke's solution for twenty-four hours were kindly tested by Dr. Eric Ogden on unanesthetized dogs and were found to possess marked pressor activity in relatively small doses. Depressor substances are also present in varying amounts along with many other substances, and considerable purification with repeated assays must be accomplished before the chemical nature of the pressor fraction is understood. Using the same method of extraction, Pickering and Prinzmetal[6] were able to find such pressor activity only in kidney cortex, but did not make tests on placental material.[7] There is also some evidence to indicate that the "placental pressor substance" may be capable of producing marked injury to capillaries.

Many of the known clinical facts regarding eclampsia may be correlated with such a postulate. A relative ischemia of the gravid uterus may, of course, result from an increased demand for blood supply, an actual decrease of maternal blood supply, or a failure of the developing uterine circulation to keep pace with the increasing demand. Multiple pregnancy or advanced hydatid mole would presumably create a greater demand and are known to be predisposing causes of eclampsia. The intrauterine death of a fetus would obviously result in a decreased placental function, and commonly results in a subsidence of the maternal hypertension.

It is well known that toxemias occur more often in primiparas, a fact which few of the present theories of eclampsia can account for. Is it not conceivable that a primigravid uterus is less capable of develop-

ing a high degree of vascularity than a uterus which has once developed a tremendous vascular bed in a previous pregnancy? If this were so, then an infantile type of uterus would further predispose to the development of a toxemia. Infantile genitalia are frequently associated with a constitutional type of woman presenting hypothyroid-hypopituitary-hypogonadal syndromes, an endocrine type known to be predisposed to the development of eclampsia.[8]

Quite obviously, the fetal demands increase with the duration of pregnancy, and similarly the incidence of toxemias increases with the duration of pregnancy. The additional ischemia resulting from uterine contractions (or from overdistention as in hydramnios) may account for the frequent onset of eclampsia during labor. The placental infarcts so commonly associated with toxemias may be manifestations of this inadequate maternal circulation. The rapid decrease in the frequency of eclampsia with each post-partum day may be similar to the rate of excretion of such a vascular toxin or to the rate of the reparative processes taking place in the liver, kidneys, brain, and other viscera. The existence of a case in which the onset of the entire toxemia syndrome occurred a week or more after delivery would be strong evidence against such a hypothesis, but a proved case of this sort is not on record.

Based on the assumption that the more adequate collateral blood supply to the pelvic organs in the lower mammals may prevent them from developing eclampsia spontaneously, experiments are under way in which the blood supply to the gravid uteri of various mammals is artificially limited. These and similar experiments should adequately test the validity of the theory. It is hoped that such suggestions may be of assistance to other investigators interested in the pathologic physiology of eclampsia.

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The author emphasizes the difficulties in making an exact diagnosis of hydatid mole before a part of the mole is expelled or removed. He therefore recommends the procedure of Albino, a puncture of the uterus through the abdominal wall. This procedure is without danger. In cases of normal pregnancy only normal liquor amnii will be obtained and no harm done. The pregnancy will continue. In the case of a mole, no fluid will be obtained even after repeated punctures.

J. P. Greenhill.

BARTHOLINITIS AND SKENEITIS DUE TO TRICHOMONAS VAGINALIS

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FOR many years *Trichomonas vaginalis* has been recognized as commonly occurring in vaginal discharge. More recently it has been observed in the male urethra and prostate, and the possibility has been discussed of the presence of the organism in the blood, tubes, ovarian cysts, and urine.[1]

It has also been suggested that *Trichomonas vaginalis* is capable of producing urethral discharge and bartholinitis.[2] In the investigation reported here, the organism has been demonstrated in Bartholin's and Skene's glands, thus suggesting a new possibility in transmission of the infestation and identifying as a pathologic entity the so-called nonspecific or nongonorrheal bartholinitis and skeneitis. Despite the common belief that bartholinitis and skeneitis are most frequently due to Neisseria infection, it has been conclusively shown in this study that the inflammation of these glands may be due to *Trichomonas vaginalis* and its symbiotic bacteria, without the presence of any of the Neisseria group.

During previous investigations of *Trichomonas vaginalis* vaginitis, edematous vulvas were noticed in the few patients who did not respond promptly to treatment. These recurrent cases were recalled to the clinic, and trichomonads were isolated from the Bartholin glands. Treatment of these glands as described below relieved the patients of the bartholinitis and subsequent insufflation of the vaginal tract controlled the vaginitis. These cases were further studied and the following information was obtained.

DIAGNOSIS

The diagnosis of the vaginal infestation has been discussed both from the laboratory and clinical aspects by many workers. The diagnosis of cases in which *Trichomonas vaginalis* is present in the glands of Bartholin or Skene is equally simple. With the patient in the lithotomy position an unlubricated speculum is inserted into the vagina. A vaginal smear, taken on a sterile applicator, is diluted with several cubic centimeters of normal saline or modified Ringer's solution,[3] and a drop of the dilution is examined under the high dry power of the microscope for trichomonas. In the cases studied in this report all were positive for vaginal trichomoniasis. The vagina and the entire external genitalia are then cleansed with an aluminum hydroxide gel and kaolin suspension, which has been found very efficient for this purpose. Then the Bartholin or Skene glands are palpated so that some of the glandular secretion is expressed. This

secretion may either be diluted with several cubic centimeters of saline in a test tube, as is the vaginal smear, or it may be placed directly on a slide and there diluted with saline. Microscopic examination is made the same way as for the vaginal smear. The methods of preparing stained specimens of cultures have been described previously.[4]

The clinical picture is typical and in most cases resembles gonorrheal bartholinitis or skeneitis. However, some of the cases show only a slight swelling of the labia and are not quite as inflamed or edematous as are the gonorrheal cases. Patients may have itching and burning of the external genitalia without the parasite being present in the vaginal secretion, with the Bartholin or Skene glands the only foci of infestation. Itching of the external genitalia, in most cases unilateral, may be considered suggestive of *Trichomonas bartholinitis* and *skeneitis*.

TREATMENT

The patients are prepared for treatment by cleansing the vaginal tract, cervix, and fornices with the aluminum hydroxide gel and kaolin suspension, in order to remove all of the mucoid material and débris. Special attention is given to the plug of mucus usually resistantly present in the cervical canal. This plug of mucus is removed by means of a sterile applicator, moistened with the suspension, which is inserted in the os and rotated between the thumb and index finger until the plug is coagulated and may be removed. In cases where the plug of mucus is closely adherent, the removal of this plug causes slight bleeding.

The infested glands are then treated by injection with 1 c.c. of 1 per cent aqueous solution of silver picrate.* As is shown in Table I, the glands in 9 patients were

TABLE I*

CASE	DURATION OF DISCHARGE AND SYMPTOMS	RECURRENCES WHILE UNDER TREATMENT FOR VAGINITIS	TRICHOMONAS VAGINALIS				NEISSERIA GONORRHEA	NUMBER OF TREATMENTS
			BARTHOLIN		SKENE	VAGINA		
			LEFT	RIGHT				
1	2 yr.	3	+	+	-	+	-	4
2	1 yr.	5	+	+	-	+	-	2
3	2½ yr.	5	+	+	+	+	+	2
4	6 mo.	3	-	+	-	+	-	2
5	3 yr.	6	-	+	-	+	-	Excised
6	2 yr.	1	+	-	+	+	-	2
7	3 yr.	2	-	+	+	+	-	2
8	4 mo.	0	-	+	+	+	-	2
9	8 yr.	3	+	+	-	+	-	5
10	1 yr.	2	-	+	-	+	-	2
11	8 mo.	3	+	+	-	+	+	Excised

*Plus and minus signs indicate that diagnosis was positive or negative in smear and culture.

injected, while in 2 patients they were excised. Two injections cleared the infestation in 7 patients. One patient required four injections and another case 5. In cases where the organisms were present in but one of the Bartholin glands, both glands were injected as a precautionary measure. Injection of the glands was followed by the silver picrate treatment for vaginal trichomoniasis. This consists of an insufflation with 5 gm. of 1 per cent silver picrate-kaolin powder, followed by a course of 6 silver picrate suppositories to be used at home by the patient. This procedure is repeated one week later.[5] In the first 3 of the 11 patients treated the

*Supplied through the courtesy of John Wyeth & Brother, Incorporated, Philadelphia.

infestation of the glands was not suspected until after several recurrences of vaginal symptoms, when the inflamed and edematous appearance of the Bartholin glands suggested that site as a focus of repeated infestation of the vagina. The other patients showing Bartholin gland symptoms were treated at the time of the initial vaginal treatment.

RESULTS

Before silver picrate treatment, the duration of the discharge and symptoms had varied from four months to eight years in the cases studied. The number of recurrences also varied. In some cases the number of recurrences may have been due to the duration of time the infestation was present (Case 5). However, in some cases the number of recurrences may have been due to the virulence of the strain of trichomonas present (Case 2).

All of the cases were positive for *Trichomonas vaginalis* in the vaginal tract. In 5 patients (Cases 1, 2, 3, 9, and 11) the trichomonads were found in both Bartholin glands; in one patient (Case 6) they were found only in the left gland, while in 5 cases (Cases 4, 5, 6, 8, and 10) the parasites were found only in the right gland. Four patients (Cases 3, 6, 7, and 8) were found to have trichomonas present in Skene's gland. Two patients (Cases 3 and 11) had in addition to *Trichomonas vaginalis* a Neisseria gonorrhea infection.

The Bartholin glands were excised in 2 patients (Cases 5 and 11), while in the other 9 patients they were injected with silver picrate. Seven patients (Cases 2, 3, 4, 6, 7, 8, and 10) were relieved of the bartholinitis with 2 injections and 1 patient (Case 1) with 4 injections; while 1 patient (Case 9) required 5 injections. Injections into the Bartholin and Skene ducts were given one week apart. Each patient was observed for a period of four months after the last treatment, and at the end of that time all were found to be negative. In none of these patients was there observed any nephritis, dermatitis, or other untoward reaction to silver picrate.

DISCUSSION

One of the outstanding obstacles in treating trichomonas infestations in the vaginal tract is reinfestation, for which several explanations have been suggested such as:

1. Reinfestation from the male.
2. Recurrence due to the organisms in the cervical plug of mucus.
3. Infestation of the glands of Bartholin and Skene.
4. Contaminated plumbing fixtures on which organisms will remain viable for as long as twenty-four hours if kept moist.
5. Reinfestation from the bladder or urethra.

Silver picrate has been used in the treatment of *Trichomonas vaginalis*[4-6] and has been shown to be highly germicidal to this organism in vitro.[7] Thus its use in *Trichomonas bartholinitis* and *skeneitis* is an extension of these former investigations.

CONCLUSIONS

1. *Trichomonas vaginalis* has been demonstrated in Bartholin and Skene's glands, and is a specific factor in producing bartholinitis and skeneitis.

2. The presence of *Trichomonas vaginalis* in these glands demonstrates that they act as foci of infestation. These glands, therefore, are one source of constant reinfestation in recurrent cases of *Trichomonas vaginalis* vaginitis.

3. Injection of the glands with 1 per cent solution of silver picrate has been found to be a satisfactory treatment for this infestation.

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LITHOPEDION DEVELOPED FROM EXTRAUTERINE GESTATION IN INTRAUTERINE AND EXTRAUTERINE PREGNANCY

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A LITHOPEDION (calcified fetus) is on rare occasions discovered during the performance of an abdominal operation, at necropsy, or by roentgenography. It may be retained in the abdominal cavity for a long period of time without harm to the mother or injury to subsequent pregnancies.

There are in the literature a number of excellent papers on the pathologic changes of this anomaly, and there are a few exhaustive reviews of the recorded cases. In 1933 Bland and others[3] reported a case and summarized 13 others which they had collected from the literature. Adding these 14 cases to the 183 assembled by Masson and Simon[18] in 1928, they estimated the aggregate of reported lithopedions at 197. In a review of the literature, from the point at which Bland and others stopped to 1937, we found 31 additional cases. These and the one herein reported bring the total number of recorded cases to 229.

Of interest in our collection of 31 cases is the fact that in 22 the lithopedion was successfully removed. As far as we could determine, there was only one death following operation. This patient[28] was a 64-year-old negress who had carried a calcified eight months' fetus as an abdominal tumor for forty years. In 3[17, 21, 25] of the remaining 8 patients no operation was performed; in 3 others[13, 19, 23] the lithopedion was not discovered until necropsy was done after death from some other condition; and finally, in 2 instances[24, 30] we had no details about the cases beyond the notation that the presence of a lithopedion had been determined. In 8 instances diagnosis was made by means of the roentgen ray.

The ages of the patients varied from 30 years[31] to 100 years,[17] and 3 patients[13, 19, 23] were in the late seventies. The period during which the lithopedion was retained varied greatly in the different cases, from four years[16] to sixty years,[17] although in the majority of the cases in this series the lithopedion was carried for less than twenty-five years. The development of the fetus, while not recorded in all cases, also showed considerable variation.

Among the cases of more than usual interest is that reported by Umnova.[29] His patient had a calcified mass removed from either side of the abdomen. Roentgenograms showed that each mass contained a lithopedion, one of two or three months' development and eleven years' duration, the other of six months' development and nine years' duration. Varchavsky and Elenevskaja[31] reported the case of a woman

who was operated upon and found to have had a bilateral tubal pregnancy with transformation into a lithopedion on one side and into a secondary abdominal pregnancy carried to term on the other side. In one case reported by Jonas[15] operation revealed an old calcified fetus in the right ovary and a smaller, more recent pregnancy attached solely to the omentum. Timko[27] and Figueroa Casas[8] each reported the removal of a lithokelyphopedion.

COMBINED INTRAUTERINE AND EXTRAUTERINE PREGNANCY

Combined intrauterine and extrauterine pregnancy (simultaneous existence of an intrauterine and extrauterine embryo) is almost as rare as lithopedion formation. While a number of reviews of the literature of this condition have been published, there is a slight variation in the computations of the different reports. The largest collection of cases was made by Neugebauer[71] who, according to Novak, assembled 244 cases from the earliest records to the year 1913. Continuing from 1913 to 1926, Novak[72] found 32 others (30 in the original paper and two postscript cases), and added two he had observed. In 1928 Stein[81] published his collection of 36 cases, including one of his own. But 17 cases he assembled were also included in Novak's group. Deducting the 17 cases duplicated by both Novak and Stein, and adding the remaining cases to those of Neugebauer, the total number of recorded cases to 1928 was 297. Gemmell and Murray,[53] in a very exhaustive review, say: "Novak, in 1926, reviewed recent cases and stated that, with those already published, the total on record was then 276. The present paper, however, while taking note of papers published up to the end of 1931, in fact only deals with 217 cases, 213 from the literature, one read at the North of England Obstetrical and Gynaecological Society, April, 1932, one reported to the Royal Society of Medicine, April, 1932, and our own two cases. Examination of the literature has made it very obvious that numerous cases have been included in reviews which were not really eligible, as for instance, twin pregnancy in a fallopian tube or simultaneous pregnancy in two horns of a bicornuate uterus, both embryos being later expelled per vias naturales. We have, therefore, limited our survey and statement of literature to cases in which we have personally studied the original article or an abstract of it. A group of 22 cases, mentioned in a later paragraph, is also excluded from the total as it deals with intrauterine and extrauterine pregnancies which were not truly simultaneous."

Because our study overlaps that of Gemmell and Murray, we have not counted cases from 1928 through 1931 included by them. We have, however, added 19 cases between those years that we could not find in their study. Our study through 1936 has added 57 cases,* including the case we report. Adding these to the 217 assembled by Gemmell and Murray, we obtain an aggregate of 274 recorded cases to the end of 1936.

It is interesting to note that in 24 of the cases we assembled, operation for the ectopic pregnancy did not interrupt the coexisting intrauterine pregnancy which in the majority of the cases terminated in normal delivery. In 3 of these cases[36, 41, 46] the intrauterine pregnancy was carried to term in spite of the grave internal hemorrhage which accompanied the operation for the ectopic pregnancy. In 25 instances, however, the concurrent intrauterine pregnancy ended in abortion, before laparotomy in 19 cases and after laparotomy in six. There was one set of intrauterine twins[80] in this group. One patient[40] died half an hour after operation for the ruptured ectopic gestation. In 2 instances[42, 68] laparotomy was done for the tubal pregnancy, but no mention was made concerning the termination of the coexisting intrauterine gestation. And in 4 cases[34, 37, 60, 64] we had no information beyond the fact that there was a combined intrauterine and extrauterine pregnancy.

*In this review, as in that of the lithopedions, it was noted that several authors mentioned cases observed by others, but did not give sufficient details or adequate references. Such cited cases were not counted. In a few instances where the cross reference could be checked, it was found that the cases had already been included in previous studies. Although we have used every available resource in our attempt to include every case, we have probably missed some.

In most of the cases the tube had already ruptured before the patient was operated upon. In a few instances[43, 47, 50, 62, 78, 84] the associated pregnancy, either intrauterine or extrauterine, was not discovered until operation was performed. Schubert[77] reported an ovarian pregnancy combined with an intrauterine pregnancy. A roentgenogram of the abdominal tumor, taken six months after the spontaneous premature delivery of a stillborn child, revealed the extrauterine fetus which was found at subsequent operation to be papyraceous and of four months' development. In one of his cases, Sunde[82] reported the delivery by cesarean section of an intrauterine infant that lived eight hours and of an extrauterine infant that lived five minutes. Weintraub[86] reported the vaginal delivery of a living, premature infant followed by the delivery of a coexisting living, deformed extrauterine child.

LITHOPEDION FOLLOWING COMBINED PREGNANCY

Combined intrauterine and extrauterine pregnancy in which the extrauterine gestation develops into a lithopedion must be extremely rare. In our search through the literature we were able to find only one case with such a sequence. It was reported by Hayward[12] in 1934.

The patient in this case was married at 16 years of age, was divorced six years later, and then remained single. Her menstrual history was normal, and was interrupted only during pregnancy and lactation which began two weeks after her marriage. After the sixth week of this pregnancy, the patient had a sudden pain in the left lower quadrant accompanied by symptoms of shock. Because of the unusually large abdomen, twins were suspected. Labor was prolonged and difficult, and resulted in the birth of only one child. The abdomen remained large after delivery, and did not regain its normal contour. One month later a diagnosis of uterine or ovarian tumor was made, and a year later the patient was told she had a uterine tumor. Because she was having no discomfort, she did not have the operation which was then advised. Twenty-six years later, when she was 43 years old, she was operated upon because of a tentative diagnosis of acute appendicitis and calcified fibromyomatous uterus. And it was during this operation that the lithopedion was found.

The case we wish to report is of the same kind. That is, we believe that our case has the criteria necessary to label it a lithopedion developed from the extrauterine gestation in a combined intrauterine and extrauterine pregnancy. As far as we are able to determine, this is the second case of this type to be reported.

CASE REPORT

Mrs. A. A., white, aged 47, entered Multnomah Hospital, Nov. 19, 1934, complaining of painful swelling of the left labia majora. The important facts in her past history were as follows: She was married in 1906. In 1908 she became pregnant for the first and only time, missing her menstrual periods in January, February, March, and April of that year. One morning while lifting, she had "labor pains" which radiated over the entire lower abdomen at fifteen-minute intervals. Eventually she passed a fetus which she saw and which her doctor said was of four months' development. Following the miscarriage she had chills and fever, and had to remain in bed for about two weeks. The doctor who attended her during this miscarriage has since died. The patient's mother, however, verified these facts.

Physical examination at the time the patient entered the hospital was negative except that pelvic examination revealed an infected Bartholin's gland cyst in the left labia and a mass, which was hard and movable, in the left lower pelvis. However, the pelvic examination was unsatisfactory because of the tenderness in the region of Bartholin's gland. The abscessed cyst was incised. Two weeks later, when the wound in Bartholin's gland had healed, another pelvic examination was made. At this examination it was found that the mass in the left lower quadrant

was movable, extremely hard, somewhat irregular in contour, and about 8 cm. in diameter. It was thought to be either a calcified ovary or an osseous formation in a dermoid cyst.

A roentgenogram of the pelvis (Fig. 1) showed a calcareous mass in the pelvis. The structures in this mass suggested a developed fetus, showing skull, extremities, and curved vertebral column with ribs. A diagnosis of lithopedion was made.

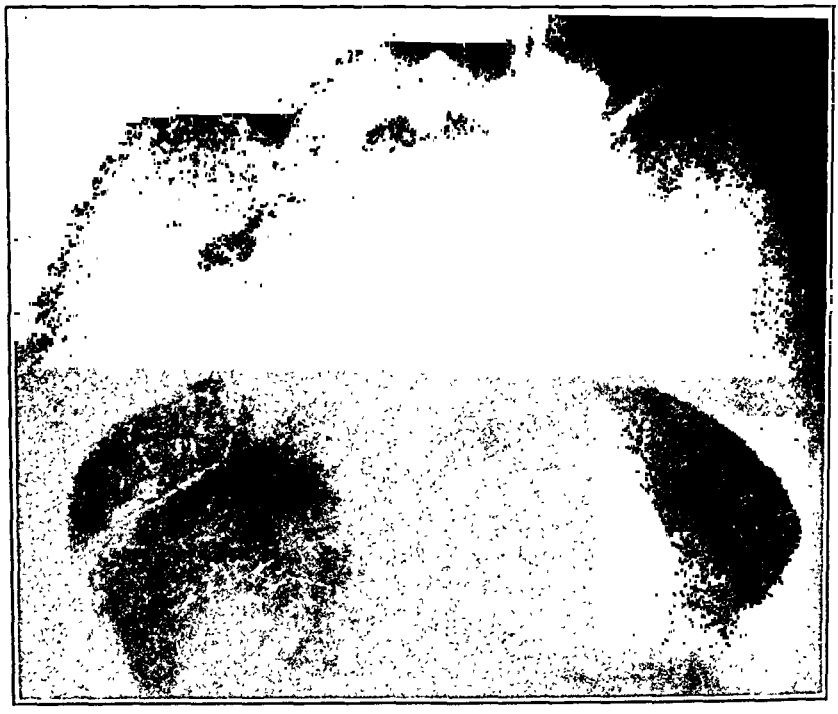


Fig. 1.—Roentgenogram showing lithopedion in the pelvis.

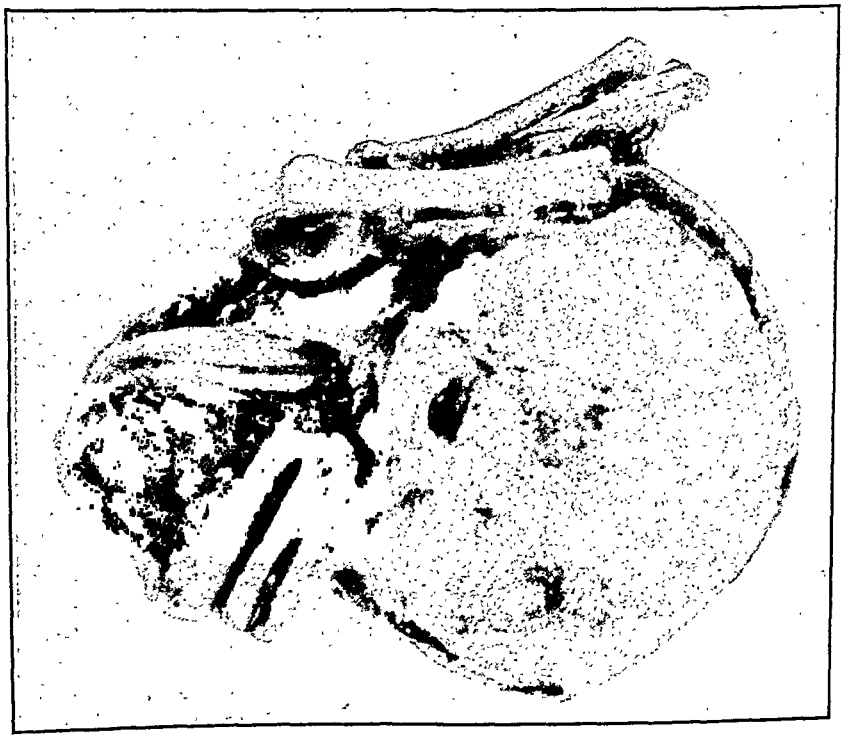


Fig. 2.—Lateral view of lithopedion.

On Dec. 7, 1934, the patient was operated upon. The abdomen was opened between the umbilicus and the symphysis. After liberating the omentum, which was adherent deep down in the pelvis behind the uterus, a calcified fetal mass was found. Its superior surface was covered by the omentum, and it was held in the pelvis by fine, cobweblike adhesions. It was, however, movable from side to side. The adhesions were broken down with the finger, and the lithopedion was easily delivered. The omentum, which was still attached to the fetal mass, was wiped off with gauze. Examination of the pelvis revealed a small fibroid on the anterior wall of the uterus. The fundus of the uterus was normal in size and position. The right ovary was normal. The right tube was also normal except for a small nodule in the isthmus. The left tube could be traced plainly from the uterus for a distance of about 3 cm., then it ended abruptly and the distal portion, with its fimbriated end, was plainly visible, completely separated from its proximal attachment and adherent to the peritoneum in the region of the infundibulopelvic ligament. When the ectopic pregnancy had ruptured, there had been a complete rupture of the tube with a separation of the segment. Further examination of the pelvis revealed a small long bone of the fetus attached to the peritoneal surface of the posterior pelvic wall. This also was removed. The patient made an uneventful recovery.

The lithopedion (Fig. 2) weighed 37 gm. It measured 6.5 by 5.75 by 3 cm. The biparietal diameters were 3 cm. and the occipitofrontal diameters 3.75 cm.

SUMMARY

1. The literature on lithopedions has been reviewed from 1932 to 1937. Thirty-one cases were found in this study. These added to the one herein reported make an aggregate of 229 reported cases to 1937.

2. A review has also been made of the literature on combined intrauterine and extrauterine pregnancy. From 1928 through 1936, 56 cases were found which, with the one now being reported, bring the total number of recorded cases to 274.

3. There is in the literature apparently only one other case of the type reported here, a lithopedion developed from the extrauterine gestation in a combined intrauterine and extrauterine pregnancy.

4. The lithopedion in the case reported at this time was discovered by roentgen ray. All evidence at hand tends to prove that the lithopedion had developed from the extrauterine gestation in a combined pregnancy, and that it had remained in the abdomen for a period of twenty-six years.

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III. Lithopedion Following Combined Pregnancy

(87) *Hayward, John D.:* See Ref. 12.

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TUBAL PREGNANCY WITH TUBERCULOUS SALPINGITIS

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A PERUSAL of the literature reveals that eight cases of coincidental tuberculous salpingitis and tubal pregnancy have been reported. In each the condition has been found at operation and established by histopathologic study. The purpose of this paper is to present a new case which is apparently the first proved case to be reported from the English-speaking world.

In the forty-seven years the Gynecological Pathology Laboratory has been in existence at the Johns Hopkins Hospital, we have had 402 cases of tuberculous salpingitis and 516 of tubal pregnancy. The case reported herein is the first in our laboratory to combine these two conditions.

The great infrequency of pregnancy in genital tract tuberculosis is in part due to the blocking off of the lumina of the tubes, both to ascending spermatozoa and descending ova. It is also due to the facts that the ova do not receive adequate nutrition from the diseased mucosa of the tube while passing down it and that the fertilized ova generally cannot become successfully imbedded in the diseased endometrium if and when they reach the uterine cavity alive (tuberculous endometritis is found in about 85 per cent of the cases of tuberculous salpingitis in our laboratory). Sterility, as is well known, is one of the symptoms of genital tract tuberculosis. A study[1] of the ovaries from women dying of pulmonary tuberculosis has shown that a high percentage of the primordial follicles are obliterated, which thus accounts for some degree of the sterility. However, in some cases,[2, 3] where the presence of tuberculous endometritis has been established by several curettements, the disease has later apparently cleared up and the women have had normal pregnancies and deliveries. The healing of the tuberculous endometritis in these cases is due both to its removal by curettement and to the regular menstrual desquamation[4] of the areas of normal endometrium where some of the tuberculous portions are shed with it. There is no opportunity for similar healing in tubal tuberculosis.

In tuberculous endosalpingitis, except where the infection is very extensive and pursues a rapid course with marked caseation, necrosis, and slough, the lumen generally tends to remain open to some slight degree, at least in the early stages. Many tubes show the familiar bulging of the ampullar portion with the contracted but patent abdominal ostium and free fimbriae giving the so-called "potato sack" appearance. Even in some cases where there is extensive caseation, the ostium and even the entire lumen may remain open. The lumen obstruction, when present, is usually found in the cornual portion of the tube and may be manifested chiefly by a tuberculous salpingitis isthmica nodosa. With healing there is scarring and thickening of the walls of the tube. As is well known, the mucosa is the original site of infection in the tube when the tubercle bacilli are blood-borne, and the spread takes place from the mucosa to the muscularis and, in severe cases, to the serosa. Histologically there are epithelioid tubercles with their Langhans' giant cells in the mucosal stroma. Around them there is an infiltration of lymphocytes. The adjacent columnar epithelium lining the lumen may show necrosis, or more usually hyperactivity with hyperplasia into several layers in depth, thus simulating the so-called "squamous metaplasia."

As some healing takes place the tips of the mucosal folds characteristically become adherent to each other and to neighboring adherent folds with the resultant

formation of many pseudoglandular epithelium-lined spaces of various sizes and shapes. Thus many "false passages" and "blind alleys" are created. In the cases of low-grade tuberculous salpingitis the healing may apparently go on at a rate equal to the spread of the infection, and many sections in our laboratory show extensive scarring of the serosal mucosa with only an occasional active tubercle. With several sections through one tuberculous tube widely differing degrees of the infection can be found, indicating that the tuberculosis may be more or less patchy in distribution. Thus, in a tube where there is slight tuberculosis of only low activity, the lumen may be open enough to allow the ascending passage of spermatozoa, while the many traps in the mucosal folds are likely to catch the descending fertilized ovum. If the mucosa lining the "trap" is diseased or scarred, the chances are that implantation cannot take place and the fertilized ovum will die. However, there is an apparent rare chance that the ovum might be caught between two mucosal folds in which the infection, for practical purposes, has cleared up. The implantation may then take place and the ovum may live and grow. The trophoblast may erode and extend through the mucosa, and since no decidua of practical importance is usually formed in the tube, the muscularis may be rapidly invaded. With the development and growth of the embryo, the expanding fetal sac becomes centralized in the lumen and continues to grow until the tube and sac rupture or the fetus dies from other causes. As a general rule, the less scarring there is in the tube wall, the greater is its elasticity and the longer and larger the fetus may grow before rupture. Since there is usually more scarring in the wall following a tuberculous infection than following a gonococcal one, earlier rupture or abortion of the tubal pregnancy will probably occur when the salpingitis is tuberculous.

* * * * *

The following is the clinical and pathologic report of a case of simultaneous tubal pregnancy and tuberculous salpingitis:

J. H. H. (Unit 77510), aged 37, married eleven years, no pregnancies. Admitted to the Johns Hopkins Hospital Feb. 12, 1937. Discharged March 5, 1937. Complaint: abdominal pain; vaginal bleeding. Family history: negative. Past history: the patient never had rugged health. Through childhood and adolescence she was so frail that her father, a physician, suspected that she had an occult form of tuberculosis, although he could never demonstrate it. She was married at the age of 26, and never became pregnant although she did not use any contraceptive measures. No serious illnesses, but always lacked strength and endurance. A highly educated woman, she has recently been working for a Ph.D. degree, but has never been able to work through the whole day. She has had to rest for an hour or two every afternoon since adolescence.

No significant or constant local discomforts. She has had mild attacks of cystitis in the last two years, due to *Staphylococcus albus* and colon bacilli. Had an appendectomy in 1921 at another hospital for chronic appendicitis, and a tonsillectomy was done in 1922.

Menstruation began at thirteen years, usual duration four to five days, with normal flow, slight pain, and no intermenstrual bleeding. The cycle has been irregular, her menses occurring every four to seven weeks. There has been frequent amenorrhea for periods of two to three months.

In this case the past history is particularly significant in that she was suspected of having tuberculosis in early life, but this was not revealed until she developed a tubal pregnancy. One of us (L. R. W.) observed this patient repeatedly during the two years preceding the operation and never suspected tuberculosis. No explanation could be found for the lack of resistance, the recurring cystitis, leucorrhea, amenorrhea and the sterility. Repeated pelvic examinations were negative. The remarkable improvement in health, gain in strength and physical endurance since the operation two years ago lead us to wonder whether this patient may not have had a latent tuberculosis of the Fallopian tubes and endometrium for many years.

Present Illness: On Dec. 13, 1936 (two months before the operation), she began to have a continuous spotty vaginal bleeding. This continued up until operation

except for a period of two weeks in January, 1937. The "menstrual" bleeding which began December 13 was thirteen days late, but this was not unusual. It lasted about seven days, after which there was only a slight daily spotting. One of us (L. R. W.) examined the patient December 29. At this time the cervix was hard, the uterus small, a small myoma was discovered, and the left adnexa were found to be enlarged to about 4 cm. in diameter. The enlargement was attributed to a corpus luteum cyst, which was the diagnosis at this time. A few days after this examination the bleeding stopped and the patient went South for a rest. There was no discharge whatever from January 8 until January 17, when the bloody spotting returned and lasted until January 23, at which time it became so definite that the patient thought she was menstruating. The flow was not as profuse as normal and lasted eleven days. During January the patient had felt well and had been free from pain.

Another pelvic examination was made on Feb. 5, 1937, when the findings were a little more definite than on Dec. 29, 1936. The uterus was still small, hard, freely movable and insensitive. At the left cornu there was some irregularity and there was a round mass low in the left fornix which was thought to be a physiologic cyst of the left ovary.

Seven days later, February 12, the patient was suddenly seized with general abdominal pain, most severe in the pelvic region. Vomiting developed in about an hour. At that time there was abdominal rigidity. A mass could still be felt in the left fornix on pelvic examination. The preoperative diagnosis was intra-abdominal hemorrhage, possibly due to a ruptured corpus luteum cyst. Temperature 99° F., pulse 88, blood pressure 100/72, white blood cell count 12,000, hemoglobin 90 per cent. Immediate operation was performed.

Operation (Feb. 12, 1937): supravaginal hysterectomy, bilateral salpingo-oophorectomy, release of adhesions. Operative diagnosis: tubal pregnancy, left, with tubal rupture; myomas of the uterus; follicular cysts of ovary, bilateral; pelvic and omental adhesions. Drains: none.

At operation about 200 c.c. of free blood was found in the peritoneal cavity. Some of it was very fresh. The uterus contained many small myomas, the largest being about 3 cm. in diameter. There were many adhesions between the omentum, the pelvic organs, and the pelvic floor. Both Fallopian tubes were open. There was a small brownish mass situated just proximal to the fimbriated extremity of the left tube, and fresh arterial blood was spurting from a fine vessel at a small ruptured point in this mass. The diagnosis of ruptured tubal pregnancy was thus obvious. Both ovaries contained follicular cysts and were about 3 cm. in diameter. The whole pelvis and all the pelvic viscera were injected. There was a diffuse injection of the pelvic peritoneum which was attributed to the irritating effect of the blood. Tuberculous salpingitis was not suspected in the operating room. Because of the pathologic condition of all the pelvic structures supracervical hysterectomy and bilateral salpingo-oophorectomy were done. No difficulties were experienced during this procedure.

The hospital convalescence was uneventful. As soon as the pathologic slides were seen the diagnosis of tuberculous salpingitis and endometritis was made. We then had the lungs examined by x-ray, and the findings were normal.

Pathologic study (Gyn. Path. No. 44501) showed (Fig. 1) the uterus to be of normal size, shape, and consistency except for a pedunculated firm nodule 2 cm. in diameter on the posterior surface and a few smaller generally distributed subserous nodules. The serosa was roughened by a few hemorrhagic adhesions. The uterine cavity was normal except that the endometrium, which averaged 2 mm. in thickness, had a slightly roughened and hemorrhagic surface. The right tube contained a small accessory ostium near the fimbriated end and was of average length and diameter except for a nodular appearance at several points; its serosa was slightly injected. On section the wall was thickened and the lumen was small but patent and filled with bloody friable substance (Fig. 1, *A*). The right ovary was about normal in size, shape, and appearance. On section it contained a few small cysts, some old scars, and a large corpus luteum of pregnancy (Fig. 1). The left tube

was of about normal dimensions except that it was nodular at points (Fig. 1, *B*). Distally it contained a globular enlargement which on section consisted of a mass of solid hemorrhagic granular substance with a small gestation sac in the center (Fig. 1, *C*). The sac wall was thin and white, the sac contained some slightly blood-tinged watery fluid and its lining was smooth and shiny. No fetus could be found. The left ovary was large and contained a follicular cyst and several small atretic follicles.

Microscopic study showed that the endometrium was thin and its stroma was fibrous. The epithelial elements were normally present. The glands were present in the usual number, were of average uniform diameter, and the epithelial cells lining them showed no secretory activity. No decidual reaction was seen. At one point the stroma contained a few definite tubercles around which there was a rather dense infiltration of lymphocytes and an occasional giant cell with coronal nuclei

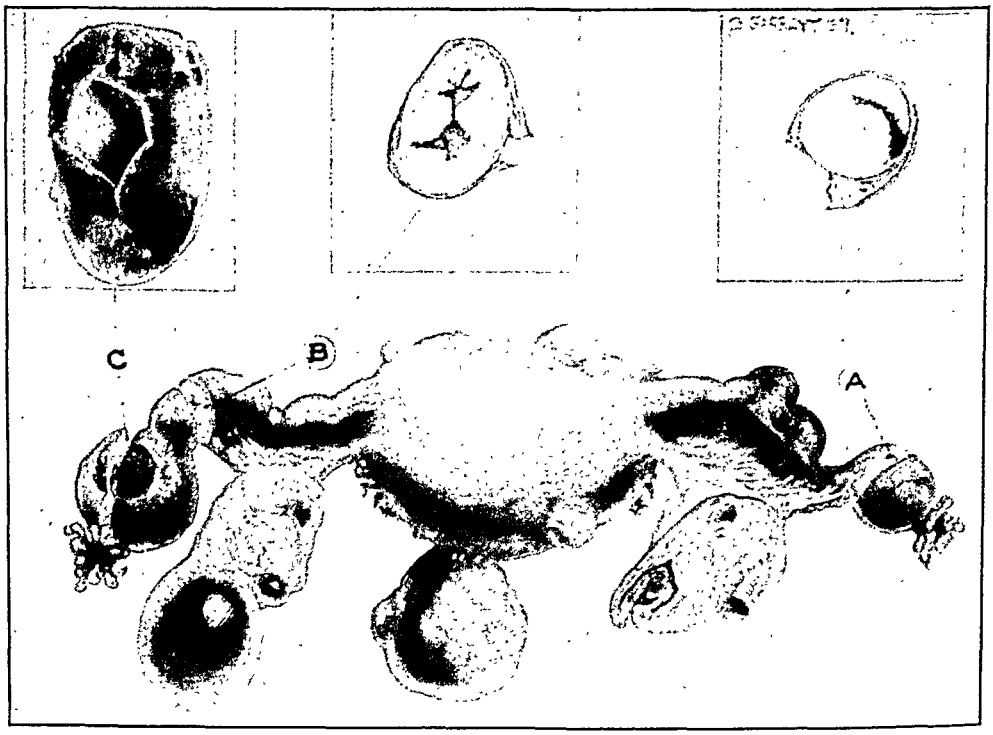


Fig. 1.—(Gyn. Path. No. 44501.) The entire gross specimen, as removed at operation, viewed from above. Note the tortuosity, injection, and nodular thickenings of both tubes, with the "potato sack" appearance of the distal ends of the tubes. The sections *A* and *B*, through the tubes, show the extensive scarring and thickening of the walls as the result of the tuberculous infection. Although distorted, the lumina remain open. Section *C* is through the pregnancy in the left tube, and shows the gestation sac surrounded by old organized blood clot and the scarred and partially necrotic tube wall.

(Fig. 2). The myometrium was normal except for a few small myomas. The serosa was slightly hypervascular and thickened. The lumen in the proximal third of the left tube was rather small and was surrounded by a thick layer of tissue made up of small cystic glands imbedded in a scarred and dense fibrous stroma (Fig. 3). The lumen and glands were lined with a single layer of columnar tubal epithelium, except for a few places where it was piled up into 2 or 3 layers. The scarred stroma between the matted mucosal folds contained many tubercles and Langhans' giant cells (Figs. 3 and 4). The muscularis was thin and intact. The serosa was thickened, scarred, hypervascular, and contained a few nests and germinal centers of lymphocytes. A section through the nodular structure in the distal portion of the left tube showed the wall to be thinned out and the serosa was scarred and infiltrated with lymphocytes. The mucosa was absent, being replaced by some scarred

and partly necrotic solid tissue infiltrated with lymphocytes (Fig. 5). A few partly necrotic chorionic villi were imbedded in the wall and normal trophoblastic epithelium covered about half of their surface. There was some slight semblance of decidual reaction around a few of the villi at the more viable points. The muscularis was sparse and infiltrated with lymphocytes. The left ovary contained Graaffian follicles, atretic follicles, and corpora albicantia. The right tube showed tuberculosis (Fig. 6) similar to that in the left tube. The right ovary contained a corpus luteum of pregnancy.

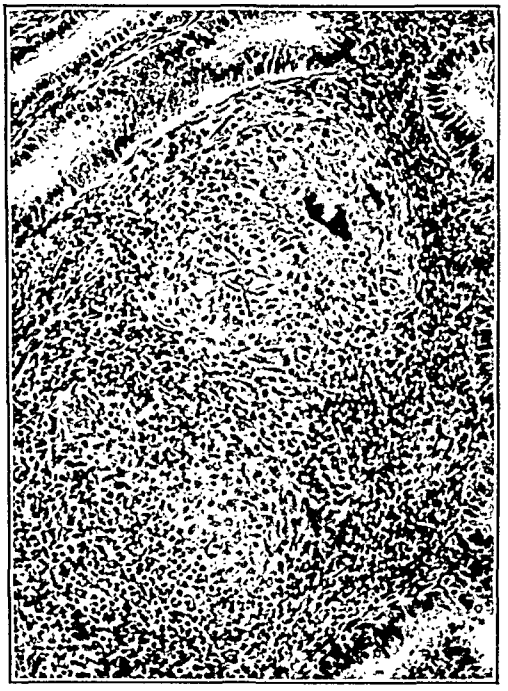


Fig. 2.



Fig. 3.

Fig. 2.—(Gyn. Path. No. 44501.) High power detail of a tubercle in the endometrium. Note also the complete absence of secretory activity and hyperplasia in the epithelium of the endometrial glands just above the tubercle. (×200.)

Fig. 3.—(Gyn. Path. No. 44501.) Section through part of the left tube at a point about 1 cm. proximal to the site of the pregnancy. The matting together of the mucosal folds with resultant cystlike spaces lined with tubal epithelium, the scarring and thickening of the mucosal stroma, and the tubercles show that the process is extensive and typical tuberculous salpingitis. (×80.)



Fig. 4.—(Gyn. Path. No. 44501.) High power detail of a tubercle in the mucosa of the left tube. Note, as in Fig. 2, the centrally located Langhans' giant cell (*A*). (×200.)

The final diagnosis was: ruptured tubal pregnancy left, tuberculous salpingitis bilateral, tuberculous endometritis, myomas of the uterus, accessory tubal ostium right, follicular cysts ovary left, peri-oophoritis chronic, corpus luteum of pregnancy ovary right, and pelvic and omental adhesions.



Fig. 5.—(Gyn. Path. No. 44501.) Section through the ruptured pregnancy near the distal end of the left tube. In the upper right corner can be seen part of the cavity of the gestation sac and its wall (*A*). Some partly necrotic chorionic villi (*B*) are seen lying imbedded in the densely scarred and chronically inflamed granulation tissue which had replaced the mucosa and most of the wall of the tuberculous tube (*C*). The avascularity of this scarred area would indicate that the trophoblast was poorly nourished. On the left is seen the scarred, thickened, and vascular serosa (*D*) (×30.)

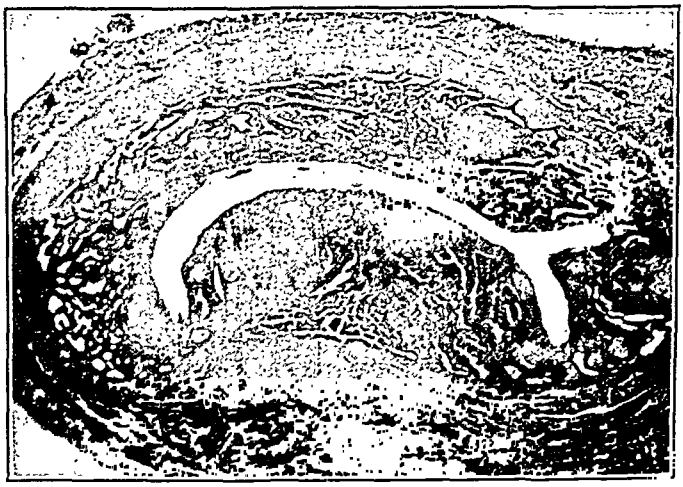


Fig. 6.—(Gyn. Path. No. 44501.) Low magnification cross section of the left tube taken about 1 cm. distal to the cornual end. Despite the extensive tuberculous process the lumen of the tube is open. At some points the lumen is lined only with chronic inflammatory granulation tissue with an ulcerated surface, and it is readily seen that a fertilized ovum passing down the tube would certainly not be in an environment favorable and nutritive to its life and development. A section from a similar portion of the right tube shows an identical picture. (×20.)

Fourteen months after operation this patient was in better health than she had ever experienced. For the past year she has had none of the old lassitude and fatigue, and no longer feels the need of afternoon rest. Although there were no signs of tuberculosis elsewhere, the patient was given careful instructions about rest, sunshine, and diet. There were practically no menopausal symptoms.

* * * * *

There are a very few cases where tuberculosis and pregnancy have been found in the same tube and in which the diagnoses have been confirmed by pathologic study of the operative specimens. In going through the literature we have found the following cases: Acconi,[5] Alexander and Moszkowicz,[6] Bovin (2 cases),[7] Ferroni,[8] Freericks,[9] Kröner,[10] and Höppner.[11] Höppner gives a very complete pathologic description of his case and a good general discussion of the subject. His patient was a 35-year-old housewife who had not menstruated for six weeks when first seen. She complained of severe acute lower abdominal pain and was in shock. A laparotomy was immediately done and the abdomen was full of blood. The left Fallopian tube contained a nodular structure about 2 cm. in diameter at the ampullar end and there was fresh bleeding from the ostium. The tube was resected and the patient made an uncomplicated recovery. Pathologic study showed some thickening of the tube at the ampullar end, and the lumen was patent. Microscopic study showed many tubercles in the masses of adherent and scarred mucosal folds, and there was a small blood-filled sac in the ampullar nodule with chorionic villi growing into the adjacent muscularis. The actual developing embryo, at about the six-week stage, was found attached to the anterior wall of the sac. There was pronounced proliferation of the trophoblastic epithelium.

In the cases of Freericks, Bovin, Höppner, and ourselves, the pregnancy was within the lumen of the tube and nidation had taken place in the general vicinity of active tuberculous infection of the mucosa. In the cases of Acconi, Alexander and Moszkowicz, and Kröner, the pregnancy was found at the ostium or cradled by the fimbriae alone. Schröder and Rau,[12] Shober,[13] Mossa,[14] and Therkelsen[15] have described cases where there was bilateral tuberculous salpingitis, and an ectopic pregnancy mass was adherent between an ovary and the adjacent tube. In the case of Schröder and Rau, the pregnancy was 6 cm. in diameter and was adherent to the mesosalpinx of the left tube and to the surface of the adjacent ovary. Despite marked fairly fresh tuberculous salpingitis, the lumina of both tubes were patent. Curiously enough the right ovary contained a corpus luteum of pregnancy and the left ovary was small and contained no cysts. This indicates (as in the authors' case) external migration of the ovum, but here it definitely was fertilized while en route. Microscopic study showed decidual changes in the endometrium and in the fimbriae of the left tube. The chorionic villi were found only in the serosa of the left mesosalpinx and tube and over part of the surface of the left ovary. Werhatzky reported a case[16] with tuberculous salpingitis in which there was an advanced abdominal pregnancy. Taylor[17] mentioned that he had found tuberculous salpingitis in 42 out of 86 cases of tubal pregnancy, but there were no pathologic studies to support this opinion. Such an occurrence is certainly contrary to the experience of all who have studied either tuberculous salpingitis or tubal pregnancy.

According to the literature, the simultaneous occurrence of tuberculosis and pregnancy in a Fallopian tube is a rarity indeed. In our laboratory only 1 in every 115 cases has been tuberculous salpingitis, while 1 in every 90 cases has been tubal pregnancy. When these two conditions themselves occur with such infrequency, the laws of chance would make their concurrence extremely rare. We have seen it but once in 46,700 cases. The chief significance of the finding of these two conditions simultaneously is the bearing out of the theory that mechanical obstruction to the descent of the fertilized ovum in the tube is the chief cause of tubal pregnancy.

SUMMARY

1. A case of simultaneous tubal pregnancy and bilateral tuberculous salpingitis is presented. It is the ninth in the world literature, and is one in which there was external migration of the ovum. The clinical and pathologic aspects of the case are treated in detail.

2. The great rarity of these cases is thought to be due to: (a) The obstruction of the lumen of the tube to any passage of spermatozoa and ova (if ovulation is taking place). (b) The lack of nutrition from the diseased tubal mucosa to the

transient fertilized ovum (with resultant death of the ovum) if the lumen is open. (c) The lack of tubal mucosa healthy enough to allow successful nidation of the fertilized ovum if it is trapped in the tube.

3. The literature dealing with the subject is reviewed.

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PRIMARY MALIGNANT MELANOMA OF THE VULVA

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PRIMARY malignant melanomas of the vulva are very rare growths. This growth may occur at any age, but most frequently occurs between the ages of forty and fifty years, usually appears as a firm, nontender nodule in the labia, enlarges rapidly, metastasizes, and ulcerates early, leaving a discharging, necrotic, ulcerated surface. It may arise from connective tissue, subcutaneous tissue, muscle of round ligament, fibroma, or other structures.

The diagnosis is made before ulceration occurs by biopsy. After ulceration it must be differentiated from ulcerated fibroma, granuloma inguinale, lymphogranuloma inguinale, and carcinoma. Malignant melanoma metastasizes by blood and lymph channels and any or all organs may be involved early. The prognosis is more unfavorable than in carcinoma of the vulva. Patients rarely live over six months, averaging less than a year. Seven per cent cures are reported in the early cases. The therapy is similar to that of carcinoma of the vulva.

The following case is presented because of the rarity of such a growth:

S. B., white, widow, 42 years of age. First admitted to Gynecological Dispensary, Louisville City Hospital, Nov. 27, 1935, complaining of a growth on the right side of vulva, nervousness, weakness. She had been married twelve years, husband died of typhoid fever. Three children, living and well; one miscarriage (five months) last pregnancy. Nine years ago, she had excision of ovarian cyst; general health otherwise good.

Menstrual history normal until one year ago; since then, every three months, and painful. Last period Nov. 20, 1935. In the past year has been taking antisyphilitic therapy, no history of other venereal disease.

Present Illness.—Sept. 25, 1935, noticed a marblelike lesion on right side of external genitalia. This has never been red or sore. After a week's growth, it broke and discharged thin, watery fluid. Since then the growth has increased rapidly in size. In the past week, has had a very odorous discharge, and has had enlargement and dull, heavy pains in right groin; nocturia and some dysuria. In past week, patient has grown quite nervous, weak, and has been unable to sleep because of pain and odor.

Physical Examination.—Nov. 27, 1935: Well-developed and well-nourished woman of 42 years. Temperature: 99.4° F.; pulse, 86; respirations, 27.

The abdomen showed a midline scar; no masses or tenderness. The right inguinal glands were the size of olives, tender, fixed and no evidence of fluctuation. Left inguinal glands enlarged, but not tender.

Large, necrosing, cauliflower-like growth, size of pint milk bottle, arising from the right labial region, involving the upper three-fourths of right labia major and minor; was fixed, and tender to touch, quite friable with three or four areas of necrosis over the surface the size of a dime; bled freely to touch; some areas were covered with a thick, necrotic membrane. Urethra was not involved, left labia apparently normal. The vagina showed congestion; cervix was essentially normal; uterus anterior and fixed; no other abnormalities made out in the pelvis.

Red blood cells, 3,730,000; white, 12,000; hemoglobin, 75 per cent; Wassermann, negative. Urine analysis: Specific gravity, 1.009, amber, acid in reaction; albumin one-plus; many red blood cells and pus (probably from vaginal discharge).

Nov. 30, 1935: Biopsy report: diagnosis, melanosarcoma, Grade IV.

Dec. 5, 1935: Right vulvectomy with resection of right inguinal lymph glands.

Operative Note.—Triangular area of the skin was removed from the right groin going wide of the involved inguinal and femoral nodes. Dissection was carried over across the center portion of the mass, down including the clitoris and right half of the mass, and circling around the urethra and including the right half of the vulva, down to within one inch of the rectum. Lateral line of incision was in the folds of the thighs. Bleeding points were coagulated and dissection of the femoral and inguinal lymph nodes was started, including the fascia of the external abdominal wall and over the region of the vulva. Dissection around the superficial saphenous vein revealed it to be involved in the growth. The wall was stripped back as far as it could be felt, but it was not deemed advisable to manipulate the vein with the possibility of dislodging the material. The involved lymph nodes were removed together with the vulva in one mass. Bleeding points were coagulated with the coagulating current after resection of the area. Skin edges were loosely approximated with kaldermal stay sutures. Retention catheter was placed in the urethra, and the patient returned to the ward in good condition.

Pathological Report.—Through the courtesy of Dr. A. J. Miller, Dr. H. Gordon, and Dr. H. H. Sweets, of the Department of Pathology, the following pathologic reports were made:

Biopsy specimen was a mass of tissue measuring 2.5 by 2 by 2.5 cm. There was no capsule. It was soft and somewhat friable. The color was gray except for brown areas due to old hemorrhage.

Sections consisted entirely of neoplastic growth (Fig. 1). The cells had round to oval nuclei which had sharp outlines and chromatin arranged in delicate strands and fine granules. In some areas the nuclei were elongated and stippled. A few have large nucleoli. A moderate number were in mitosis. The cytoplasm stained densely with eosin. A few cells were polygonal, but most of them were stellate or elongated, resembling somewhat the shape of smooth muscle cells; others had long, coarse processes. Occasional cells were huge and some of these were multinucleated. There were a few small scattered areas of pigment deposit, some of which was evidently derived from hemoglobin, but some was questionable. Special stains for iron revealed small, fine, granular masses of brown pigment in some of the cells. It was, therefore, considered as melanin.

The cells were arranged in interlacing bundles. There was no palisading. The stroma was very small in amount except for a few large trabeculae. There were numerous small blood vessels which consisted of an endothelial lining supported by a very small amount of connective tissue. The parenchymal cells were sometimes arranged radially about the strands of stroma.

The specimen was an elliptical piece of skin including part of the vulva and to which was attached an ulcerating tumor mass, subcutaneous fat, fascia, and several lymph nodes. The tumor measured 11 by 6 by 4 cm. and had ulcerated the skin. It was light gray in color except for localized yellow areas due to necrosis and

brownish portions where hemorrhage had occurred. The lymph nodes were large, firm, and light colored as if invaded by tumor growth.

The microscopy was identical with that of the previous specimen except that there were a few more mitotic figures, the structure was a little more cellular, and there was less fibrillar substance. There was infiltration at the periphery of the growth, but the border was quite definite and there was some pressure atrophy about it. The pigment was small in amount, but was demonstrable (Figs. 2 and 3).

The ulceration of the skin had resulted from invasion by the tumor. There was no suggestion that the squamous epithelium or that of the skin glands was the source of the tumor. The lymph nodes were partly destroyed by metastatic growth.

Dec. 6, 1935: 100 r. daily x-ray treatment for twenty days: Posterior pelvis, 1,400 r.; anterior pelvis, 1,400 r.; total, 2,800 r.

The patient made a most satisfactory convalescence; the wound healed well; the patient was discharged from the hospital on Jan. 2, 1936, in good condition. She was entirely free from pain in the groin, gained in weight and was up and about her work in usual health until May 7, 1936, when she noticed a lump appear just

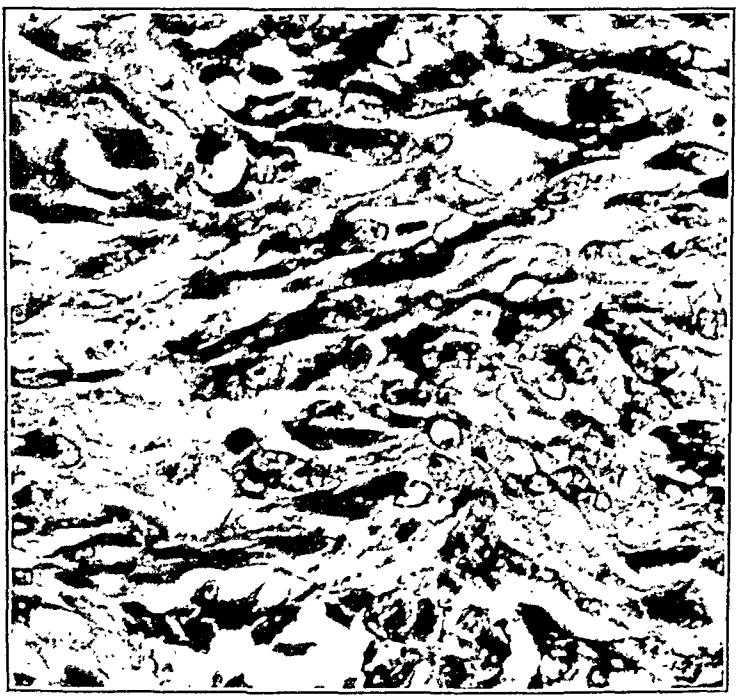


Fig. 1.—High-power photomicrograph of primary tumor. The cells have eosin-staining cytoplasm which is elongated and continuous with that of adjacent cells. A very few small granules of melanin were found.

under the eleventh rib, right axillary line. Examination showed subcutaneous mass 6 cm. in diameter at the right eleventh costal margin, with enlargement of mass in right inguinal region. There were some small shotlike glands in the right axilla.

May 18, 1936: X-ray films showed that the patient had extensive metastatic masses throughout both lung fields, and eleventh and twelfth ribs, right, with rapidly growing recurrence in right groin and areas over the chest wall.

June 14, 1936: Patient died at 1:35 A.M. following convulsive seizure with generalized metastasis.

Autopsy.—The body was in a fair state of nutrition. In the region of the right mid-axillary line at the level of the tenth rib was a tumor mass measuring 8 by 3 cm. It was not attached to the rib or the skin and was slightly soft. A number of masses were palpable in the right lower quadrant and there were enlarged firm lymph glands in each groin. The wound was well healed and no tumor was found in the scar.

There was some displacement of the liver downward, the lower border being 8 cm. below the ribs in the midclavicular line. Each diaphragmatic dome was lowered slightly. Beneath the periosteum of the bodies of the seventh and eighth thoracic vertebrae and also beneath the periosteum of the right second, third, fourth, and seventh ribs, there were tumor masses 1 to 3 cm. in diameter, firmly embedded in the tissue and invading the bone.

The heart weighed 250 gm. There were a few petechiae in the pericardium. The mitral leaflets contained two small sclerotic plaques, but they caused no demonstrable interference with function.

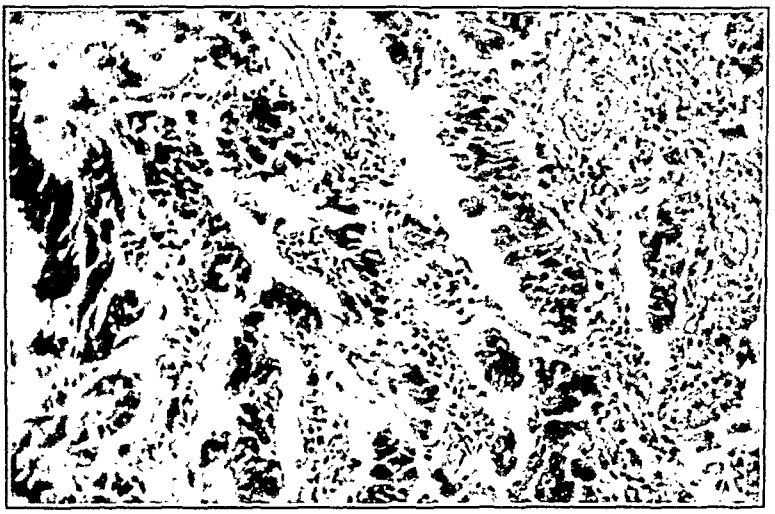


Fig. 2.—Low-power photomicrograph of lung metastasis. Several alveoli contain masses of tumor cells which are grouped to resemble epithelium.

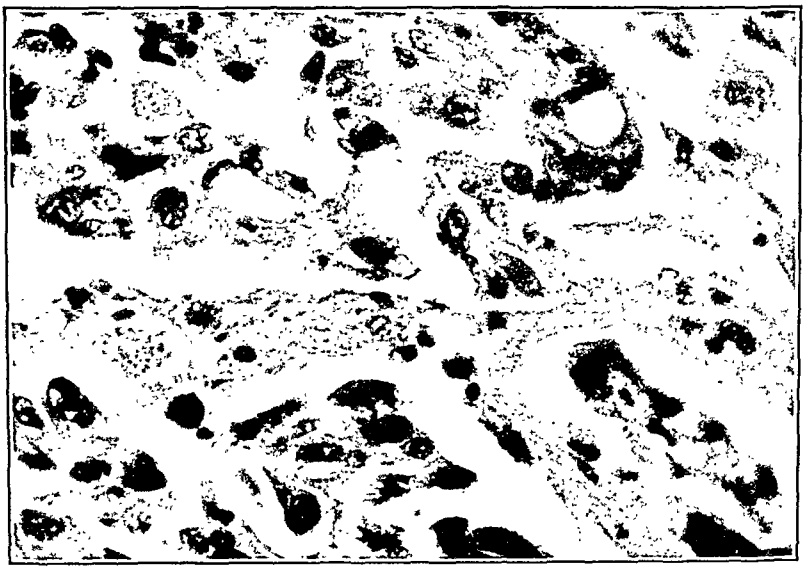


Fig. 3.—High-power photomicrograph of brain metastasis. The cells here have less cytoplasm, and are less uniform. Granules of melanin can be seen in the cytoplasm of several cells.

The nuclei of the muscle cells were pyknotic and there was moderate cloudy swelling.

The right lung weighed 380 gm., the left 400. There was slight edema in the posterior portions. Throughout the substance of each lung there were numerous tumor nodules, 1 cm. or so in diameter. They were yellow gray in color, soft, the sectioned surfaces were blotched with old hemorrhage. The central portions were

necrotic. The central part of the left lower lobe was soft, greenish in color, and smelled putrid. Partial obstruction of the bronchus, by a large neoplastic lymph node at the hilus, had evidently contributed to the gangrene. Most of the hilus nodes were enlarged by tumor growth so that they measured from 1 to 3 cm. in longest diameter.

Sections of the lung revealed microscopic abscesses evidently contributed to by pressure from the tumor nodules. The tumor nodules were rich in parenchyma cells which, at the periphery of the growths, were growing in the lumina of the air sacs with no new stroma at all. The cells were elongated, had a moderate amount of eosin-staining cytoplasm with a very few stubby processes. They were in compact masses with imperfect palisading. Occasionally there were layers of columnar cells arranged like epithelium. Mitotic figures were in moderate numbers. Small masses of brown pigment (melanin) were frequently seen in the cytoplasm. There were a few tumor giant cells. In the center of the nodules the lung was destroyed and a small amount of new stroma had developed.

The liver weighed 1,950 gm. The organ was strewn with tumor nodules varying from those barely visible to others 1.5 cm. in diameter. They were under some pressure. The liver substance was light colored, soft and was moderately mottled from chronic passive congestion.

Sections revealed neoplastic structure identical with that in the lung except there was more stroma, giant cells were more numerous, and melanin was abundant. There was some pressure atrophy about the growths. There was slight damage from passive congestion.

The spleen weighed 400 gm. The substance was soft. Throughout the tissue 15 tumor masses 1 to 4 cm. in diameter were found, 4 of these were present in the capsule.

The structure of these nodules was identical with those elsewhere.

The kidneys weighed 180 gm. each. In the cortical substance of each organ there were several tumor masses, each of which was a few millimeters in diameter. In the upper pole of the right one a tumor 1 cm. in diameter was found.

Sections showed the tumor to be the same structure with a small amount of melanin. The tubule cells were moderately damaged by cloudy swelling.

The left adrenal was normal in size, but its sectioned surface showed it to be partly replaced by a tumor tissue. The right one was enlarged by a tumor mass 5 cm. in diameter which evidently began in the medulla and expanded the adrenal so that the gland tissue formed a capsule.

This tumor was identical with the others. Melanin was abundant.

The lymph nodes of the abdomen were enlarged moderately, especially those in the region of the pancreas and the sentinel node of the gall bladder.

Sections showed these to be badly damaged, some to be completely replaced by tumor growth. Here the tumor cells were arranged about the blood vessels. Pigment was present.

The gastrointestinal tract and pancreas contained no tumor tissue. The appendix had been removed surgically.

The uterus was small. In the wall of the body was a hard, spherical, encapsulated tumor mass 5 mm. in diameter, evidently different from the other tumors found.

Sections of this tumor showed it to be made up of interwoven bundles of smooth muscle fibers identical with those of the uterine muscle. There were also numerous glands lined by tall columnar epithelium and supported by stroma similar to that of the endometrium. The structure was that of an adenomyoma.

The right uterine tube and ovary were absent evidently from surgical procedure. The left tube and ovary, the bladder, and pancreas appeared normal.

The thyroid gland showed no changes grossly, but sections revealed several tumor thrombi in large veins and capillaries. The cells were the same type as those in other tumor nodules, but were pyknotic. There was no stroma. It appeared that the masses in the veins were extensions from those in capillaries, though the gland was not invaded.

In the skull at the vertex there was an irregular opening about 8 mm. in diameter. Just beneath this was a tumor mass 2 cm. in diameter. The defect was the result of tumor growth beginning beneath the dura and invading the bone. In the left parietal region was a second extradural tumor 1.5 cm. in diameter, but the inner table of the skull was only roughened.

The convolutions of the brain were moderately flattened from pressure. In the leptomeninges were numerous dark spots resembling old hemorrhage. Coronal sections revealed numerous tumor masses in the cortex, white matter, in the pons and cerebellum. These varied in size from those barely visible to 8 mm. in the pons and 2 cm. in the cerebellum. The tumor was soft, gray, friable tissue into which some hemorrhage had occurred.

Sections revealed the same structure here as elsewhere, except the cells resembled epithelium more, and melanotic pigment was very abundant. There was no new stroma. A number of blood vessels had extensions of tumor growth about them in the perivascular lymph spaces. There was much hemorrhage in and about some of the growths.

SUMMARY

The primary illness consists of a malignant melanoma arising in the skin of the right labia majus, extending into the subcutaneous tissues, to the skin of the pubic region and vulva, and metastasizing to the regional lymph nodes, lymph nodes of the abdomen and chest, liver, spleen, adrenals, kidneys, lungs, brain, and skeleton.

The derivation is, by reasoning and not by demonstration, from the chromatophores of the skin. The immediate cause of death is pulmonary infection consisting of small multiple abscesses near metastatic tumor growths and gangrene of the left lower lobe contributed to by partial obstruction of the bronchus by a large neoplastic lymph node at the hilus.

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908 BROWN BUILDING

Marcel, J. E.: Gonococcus Vulvovaginitis in Young Girls and Its Treatment, Rev. franç de gynéc. et d'obst. 33: 396, 1938.

Marcel is of the opinion that gonorrheal vulvovaginitis in young girls is more than a vulvovaginitis because it involves the ureters, the cervix and sometimes also the rectum. The disease is not rare. It has a definite social importance because it may interfere with the future genital life of the child.

Local therapy requires a long time, it is difficult and has many failures. Estrin therapy has not yet become popular in France in spite of its successes, especially in the acute cases.

J. P. GREENHILL

PRIMARY LYMPHANGIOMA OF THE FALLOPIAN TUBE

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PRIMARY lymphangioma of the Fallopian tube is a rare neoplasm. Complete review of the literature discloses 17 cases reported to date.[1-14] Of these, only 3 are found in American Journals.[5, 8] Moreover, of practical importance is the histologic interpretation of certain tumors, classified as lymphangioma, in regard to potential malignancy. We, therefore, wish to present the pathologic findings in an additional case of primary lymphangioma of the Fallopian tube.

Clinical History.—M. T., a white, married woman, 55 years of age, was admitted to the Buffalo General Hospital July 8, 1937 in the service of Dr. Ralph Upson complaining of "a tumor in the abdomen" for one and one-half years. With appearance of the tumor, the patient experienced a heavy sensation in the lower abdomen. There had never been definite pain. Frequency of urination and nocturia were present. In the past year the patient had lost 12 pounds in weight.

Except for a normal delivery in 1911, the obstetric history included no other pregnancies.

Menstruation began when the patient was fourteen years of age. Periods were regular, every twenty-eight days and four or five days in duration. After the abdominal tumor was noticed, periods became irregular. There was menorrhagia and metrorrhagia. The last menstrual period occurred June 25, 1937. The mother of the patient died of a growth in the abdomen.

Physical Examination.—Temperature, pulse, and respiratory rates were normal. The patient was a well-developed, white woman, apparently in good health. Lungs were clear and resonant. Heart rate was regular; no murmurs were heard. Abdomen showed no scars. In the lower half, there was distinct bulging. Here palpation revealed a large mass, which was irregular, hard, and movable.

Laboratory Work.—Urinalysis, serologic and blood chemistry examinations disclosed no relevant findings.

The clinical impression was fibroid uterus.

Operative Report (Dr. Ralph Upson, July 9, 1937).—Low midline incision. A large, grapefruit-sized fibroid uterus was found. One fibroid on the posterior surface, which extended deeply into the pelvis, was adherent to the rectum and had to be dissected therefrom. The left tube and ovary were also bound by adhesions. Hysterectomy with left salpingo-oophorectomy was made. The right tube and ovary were apparently normal.

Postoperative Course.—Following operation, the patient developed purulent drainage from the abdominal wound, which gradually subsided. Patient was discharged from hospital Aug. 2, 1937.

Gross Description of Surgical Specimens.—Corpus uteri with attached left tube and ovary was received. The corpus was myomatous. It weighed 850 gm. and measured 19 by 13 by 8 cm. The gross structure was distorted by multiple fibroids. The 3 largest were intramural and measured 4, 6, and 7 cm. in diameter. In the fundus was a walnut-sized fibroid. Several smaller submucous and intramural fibroids were scattered throughout. The endometrium was not hyperplastic; it measured 0.2 cm. in thickness.

The ovary measured 4 by 3 by 1 cm. It contained a corpus luteum with central hemorrhage and a corpus hemorrhagicum.

The Fallopian tube was 11 cm. long. The fimbriated end was patent. At a point 8 cm. from uterine attachment, there was observed in the upper wall an apparently

circumscribed nodule 1.1 cm. in diameter. The overlying peritoneum was stretched, smooth, and glistening. The nodule was solid and cut with moderate consistency. On section the nodule bulged outward. The color was whitish. The cut surface had a peculiar "papillary" or pitted character. The lumen of the tube at the site of the nodule was markedly compressed. In the remainder, the wall of the tube was not thickened; the lumen contained no exudate.

Histologic Description of Surgical Specimens.—Microscopic examination of uterus and ovary confirmed the gross findings. Fibroids were typical leiomyomas.

The nodule in the left Fallopian tube was fixed in 10 per cent formaldehyde and imbedded in paraffin. Sections were cut at 5 and 7 micra. Hematoxylin-eosin, Van Gieson, Mallory anilin blue-acid fuchsin, Weigert elastic, mucicarmine, and thionine blue staining and modified Bielschowsky silver impregnation methods were carried out.



Fig. 1.—Gross appearance of lymphangioma of Fallopian tube.

On microscopic examination, the nodule, noted grossly, was situated in the wall of the tube between tunica propria, muscularis and subserosa. The muscle layer was practically completely replaced; only at the outer parts of the nodule could a few muscle fibers and bundles be seen. Though, with low power, the nodule appeared somewhat circumscribed, it was not encapsulated. Its borders merged actively into surrounding tissue of tube.

In general, the histologic picture of the nodule itself was that of a meshwork of channels or spaces ranging from capillary to cavernous in size with moderate stroma. The large spaces were distributed chiefly in the central portion. The representative lining of spaces consisted of single flat endothelial cells. For the most part the nuclei were slightly plump, oval with their chromatin material arranged in fine dots. Some nuclei were thin and hyperchromatic. There were no prominent nucleoli. In certain spaces the lining in addition to typical endothelial elements possessed cuboidal and polyhedral cells. Their cytoplasm stained lightly and was fairly abundant. Nuclei were moderately large and oval. Cell outlines were not distinct. Free margins were not sharp but feathery; cytoplasmic festoons of syncytial nature projected into lumens. True cilia were not seen. In many spaces the lining was composed entirely of tall (cuboid-cylindrical-polyhedral) cells such as just described. Not infrequently these cells appeared stratified. They also exhibited budding proliferation into lumen. Few lumens were nearly filled with desquamated and proliferating cells. The rather frequent presence of endothelial giant cells in the lining was also noted. Lining cells also showed atypical nuclei.

The lumens were for most part free. Or they contained a thin slightly acidophile fluid and cells with round or indented nuclei. Rare eosinophile cell was seen. In many lumens cells corresponding to desquamated endothelial cells were observed.

Mucus stains (controlled by sections from normal appendix, under same fixation) were completely negative for mucus both in cells and in lumens.

The stroma in certain areas was edematous. In other parts it was dense and cellular. The cells were not fibrocytes, but were elements concerned with the tumor itself. The appearance of the stroma imitated the structure seen in angioblastic and reticulo-endothelial neoplasms. The cytoplasmic outlines of the cells referred to could not be distinctly made out. The cells were moderately large and oval and polyhedral in shape. They could be recognized by large, oval faintly staining nuclei. Syncytial processes with reticular connections between cells were evident. Cells were also arranged in solid masses and cords. Canalization was sometimes taking place.

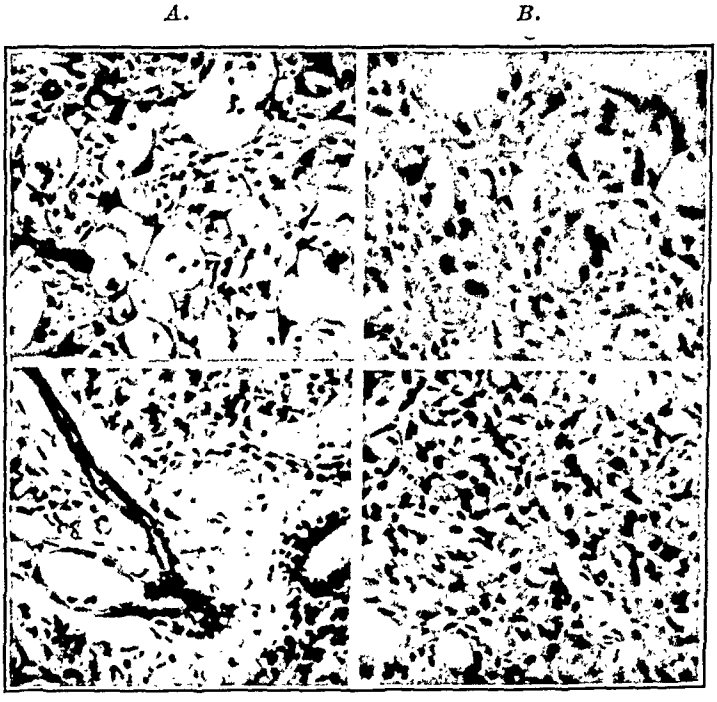


Fig. 2.—*A*, Spaces lined by endothelial cells with round cells and desquamated endothelial cells in lumens. Endothelial giant cells are shown. (High power.) *B*, Spaces show tall and large cells with huge dark, and multiple nuclei. (High power.) *C*, Tumor growing into mucosa, showing lymphatic space contrasted with 2 glands. (High power.) *D*, More cellular part of stroma with capillary formation. (High power.)

Cytoplasm of cells in stroma exhibited rare vacuolation. The number of collagen fibers in the stroma was small. Most of the fibers were reticular and elastic in nature. The reticulum fibers did not surround spaces as a definite basement membrane but encircled them, and continued as reticulum fibers of the stroma, running between cells. Scattered in stroma were round cells, eosinophiles and neutrophiles. In one area of the nodule there was focal infiltration, in addition, of plasma cells and hemosiderosis. The stroma possessed small arteries and thin-walled blood capillaries of its own.

The mucosa overlying the tumor was stretched. Epithelial cells were columnar, cuboidal, and flat. Villi were preserved only in a few places. Tunica propria of these showed a few round cells; beneath the stretched mucosa there was infiltration of round cells, and neutrophiles, edema and recent hemorrhages. Few glands extended into tunica propria. The distinction between tumor spaces and glands was not difficult.

In outer part of tumor were focal collections of round cells in a network of reticulum. The growth, as previously described, invaded both mucosa, subserosa, and adjacent muscle fibers. No calcification was observed.

The histologic diagnosis was lymphangioma with distinct endothelial proliferation. Because of this proliferation, together with replacement of muscle fibers and invasion into mucosa and subserosa, it was felt that the tumor had to be considered malignant from an histologic aspect.

COMMENT

We feel that the lesion of the Fallopian tube which we describe is justifiably diagnosed as lymphangioma for various reasons. Grossly, it forms a definite, more or less circumscribed nodule within the wall of the tube. Microscopically the fundamental structure is one of small and medium-sized spaces which are lined by flat endothelial cells, and which contain no erythrocytes, but for the most part mononuclear cells, and thin fluid. Endothelial giant cells are seen. The stroma possesses a cellular architecture seen in angioblastic tumors. Its fibrillar element is composed chiefly of reticular and elastic tissue. Collagen fibers are sparsely distributed. The reticulum which surrounds spaces does not form a strictly defined basement membrane, but blends continuously with reticulum in stroma. Interstitial round cell infiltration is present; finally, follicular collections of round cells with reticular network appear in peripheral zone of the nodule.

Of practical interest, from the standpoint of histologic diagnosis, is the presence of cells in the lining of a good number of spaces which are much taller than flat endothelial cells. Though at first glance such a feature might lead one to search for an epithelial character in the neoplasm, we believe that this microscopic finding may be honestly reconciled with the diagnosis of lymphangioma. For, on close examination, "tall" cells are discovered only in a portion of spaces, or along with flat cells in the lining of a single space. The minute structure of these cells and their relation to exfoliated cells in lumens, to the stroma, and to glands of mucosa do not support an epithelial origin. With controlled staining methods mucus could not be demonstrated within lining cells or in lumens. In addition, histologists accept the view that endothelial cells harbor the biologic propensity to assume varying gradations of tall forms. Such conversion manifests itself in inflammatory and neoplastic processes in endothelium of lymph and blood channels. Cuboidal and cylindrical cells have been described in previous cases of lymphangioma of the Fallopian tube, notably, those of Höhne,[1] Dienst,[2] Kermauner,[3] Franz,[4] Dietrich,[7] Schiffman,[12] Nicod,[13] and Szathmáry.[14]

Of further practical interest, not only from the point of view of histologic diagnosis but also from the basis of prognosis, are certain microscopic evidences of endothelial proliferation, besides change in height of lining cells, e.g., stratification and desquamation of lining cells, atypical nuclei, giant cells, and blastoma-like stroma with solid nests and cords, apparently undergoing canalization.

Although any of these may be seen some time in simple, mature lymphangiomas, they must be interpreted, when found to an appreciable extent, as speaking for an embryonal, actively proliferating tendency. As a matter of fact, Kermauner wondered whether the degree of endothelial proliferation, which he considered was especially marked in his case, and in the two instances reported before him did not warrant placing so-called lymphangioma of the Fallopian tube in the category of endothelioma. Since Kermauner's paper, however, out of 10 cases[5-7, 12] with adequate histologic descriptions have shown rare or no signs of endothelial proliferation. Indeed, review of the literature reveals that lymphangioma of the Fallopian tube can be classified into two histologic groups: (1) lymphangioma with rare or no endothelial proliferation (2) lymphangioma with slight to distinct endothelial proliferation (lymphangio-endothelioma?).

That the discussion of the foregoing paragraph involves something more than a hair-splitting distinction is borne out by two statements. In every case of lymphangioma of the Fallopian tube reported in the literature, which showed rare or no endothelial proliferation (despite destruction of tubal tissue and lack of encapsulation), the neoplasm was considered innocent. In certain cases,[1-4, 11] on the other hand, with acknowledged endothelial proliferation this finding along with that of

replacement or destruction of normal tissue of the tube and with that of mergence or invasion into surrounding issue was taken as histologic ground for expression of an opinion of "malignancy." Now what meaning shall be placed on such histologic evaluation in regard to the practical problem of clinical prognosis? In answer to this question, we must note that the cases definitely appraised as histologically malignant possessed certain features grossly which bespoke a localized lesion. The tumor was small. It was discovered only as an incidental finding in women operated upon for other causes. The peritoneum overlying the tumor was not perforated. Metastases were not found. Whether patients, subsequent to extirpation of these small lymphangiomas, followed the course of a benign tumor, as suggested by the gross findings, or of a malignant blastoma, as adjudicated by microscopic examination, cannot be determined because of the total lack of follow-up reports in the literature. In Aschheim's third case where besides showing destruction of muscularis and mucosa, the lymphangioma approximated a child's head in size, gave symptoms and physical signs, and evoked a gross impression of malignant tumor, the patient was entirely well one year after excision. Kermauner's suspicion, however, that perhaps some cases labeled "carcinoma of the Fallopian tube" might actually be endotheliomas has to be mentioned. In view of the facts, then, that only a few cases of lymphangioma of the Fallopian tube with acknowledged endothelial proliferation have been recorded, and that information relative to postoperative course in these cases is lacking, the problem of correlating histologic findings with clinical prognosis must be left open. One can yet speculate, as apparently Schiffman[12] and Szathmáry[14] did, whether the tumor under discussion may not be of a type which calls forth an histologic opinion of malignancy but which, at least, in the stage thus far seen, and with regard to metastases, acts biologically in a benign manner.

On the other hand, Nicod[13] precludes the necessity of a consideration, such as outlined in the preceding paragraph, by classifying recorded cases of so-called lymphangioma of the Fallopian tube so that neoplasms with endothelial proliferation are separated from simple lymphangiomas and designated "reticulomes" or "reticuloendotheliomas." For Nicod,[13] these tumors comprise a distinct pathologic entity. Originating in mesenchyme with angio- and lymphoblastic potentialities, they occur in the Fallopian tube and in the male genital organs, and run a silent, benign course.

In the seventeen recorded cases of primary lymphangioma of the Fallopian tube, the race was apparently always white. Where information was given, the ages ranged from 30 to 86 years. Six patients were more than 50 years old.[4, 8, 10, 12, 13, 14] The tumor occurred in nulliparas[4, 9, 14] as well as in multiparas.[3, 7, 11] In 14 cases, it was discovered incidentally at operation for pelvic lesions which produced symptoms, e.g., leiomyoma of uterus,[1, 2, 3, 5, 9, 11, 14] carcinoma of ovary[12] and uterus,[4] fibroma of ovary[8, 9] and retroflexed uterus;[7, 8] in 2 cases,[10, 13] at autopsy, in patients who died from cardiac decompensation. On one occasion[9] the lymphangioma reached a size large enough to call for surgical therapy. The isthmic, middle and ampullary parts of either tube were fairly equally involved. The pathologic findings in our case can serve to illustrate the average gross and histologic description from the literature. In 2 cases[3, 13] calcification was noted microscopically.

Theories concerning the etiology and pathogenesis of primary lymphangioma of the Fallopian tube are purposely omitted from our paper. In regard to them reference can be made to the reports of Silva[10] and Nicod.[13]

SUMMARY

The literature on primary lymphangioma of the Fallopian tube, which includes 17 cases, is reviewed. The pathologic findings in an additional specimen, found accidentally in the left salpinx of a 55-year-old white, married woman operated upon for a fibroid uterus, are described. Attention is drawn to the histologic classifications of lymphangioma of the Fallopian tube on the basis of descriptions of the recorded cases. The importance of correlating these classifications with pathologic and clinical

data in future cases from the points of view of histogenesis and biologic behavior of the neoplasms under discussion is implied.

We are indebted to Dr. Ralph Upson for permission to transcribe the clinical record.

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PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

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THE first authentic case of primary carcinoma of the Fallopian tube was described in 1888 by Orthmann.[1] It is a rare disease, only 3 cases occurring in 30,000 gynecologic admissions in the Bellevue Hospital in New York.[2] Charache[3] in 1936 reviewed the literature from 1888 to 1935 and discovered only 323 cases. It is therefore of more than usual interest that we encountered on the Public Ward Service of the Toronto General Hospital 2 cases within a period of fourteen months.

Case 1.—*Primary bilateral carcinoma of Fallopian tubes.* The patient, Mrs. T., 57 years of age, was admitted to the Toronto General Hospital in September, 1933. Her chief complaints were irregular slight vaginal bleeding of four months' duration. The menopause had occurred seven years previously. She had had one full-term pregnancy thirty-two years ago, followed by pain in lower abdomen which gradually disappeared in the ensuing years. There were no further pregnancies. The patient's mother died from carcinoma of the breast.

Physical examination revealed a healthy-appearing white female looking much younger than her stated age. Abdominal examination was negative except for slight lower abdominal tenderness on deep palpation. Pelvic examination revealed atrophic external genitalia. The cervix was slightly eroded and a small polypus protruded from the external os. The body of the uterus was slightly irregular in shape. A cystic mass the size of an orange was palpated in the right fornix. No mass was felt in the left fornix.

A preoperative diagnosis of cervical polypus and ovarian cyst was made and a provisional diagnosis of carcinoma of the endometrium. At operation the cervical polypus was removed, the cervix dilated, and the uterine cavity curetted. Small thin fragments of endometrium were obtained. The cervix was cauterized. The abdomen was opened and the uterus found to contain small myomas. Both tubes were closed, retort-shaped and adherent to the ovaries. The right ovary was replaced by a cyst the size of an orange. Bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed. The patient made an uneventful recovery and left the hospital apparently well in seventeen days.

Pathologic Report.—Specimen: Uterus, tubes, ovaries, polypus.

Gross Description: A small uterus 4 cm. in length with atrophic wall in which three small myomas were present, the largest measuring 1.5 cm. in diameter. One

was calcified. The left tube was thin-walled with lumen dilated to a diameter of 1.5 cm. and was filled with a grayish colored, papillary friable growth attached to tubal wall throughout its whole extent except in the isthmic portion. The fimbriated end of the tube was closed. The right tubal lumen was dilated to a diameter of 3 cm. and was filled with a similar growth. The right tube was adherent to the ovary and the fimbriated end was closed. The ovary was replaced by a cyst 6 cm. in diameter, filled with clear fluid, and lined by a smooth glistening lining. Left ovary was atrophied.

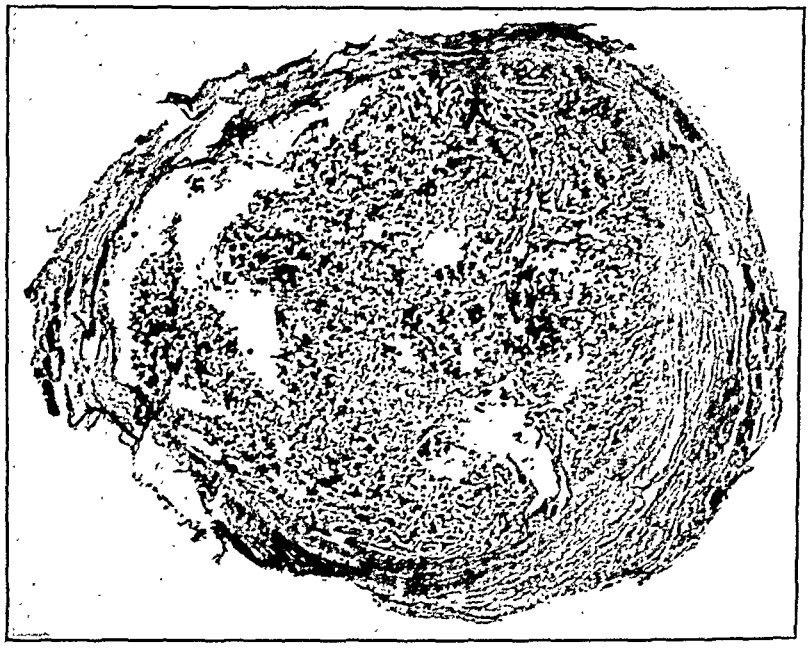


Fig. 1.—Case 1. Very low power of cross section of tube, showing general lacelike pattern of the carcinoma.

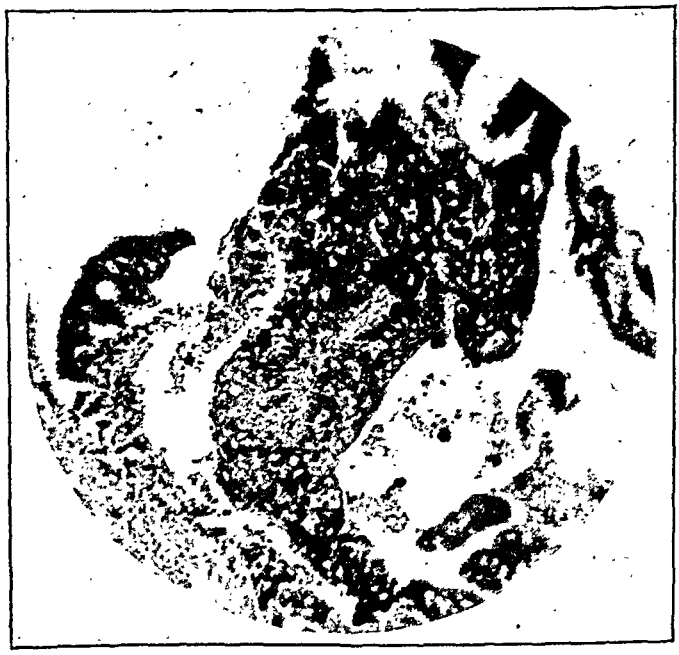


Fig. 2.—Case 1. Microphotograph medium power, showing piling up of malignant cells supported on a scant delicate stroma.

Microscopic Report.—The uterine muscle bundles and endometrium were atrophic. The myomas presented the usual microscopic picture. The polypus had a fibrous tissue stroma studded with multiple gland spaces lined by typical endocervical epithelium.

Both tubes showed lumen dilated by a papillary overgrowth of tubal mucosa, the papillas of which in many areas had fused together, giving a lacelike pattern to the growth (Fig. 1). Cells in some areas closely resembled tubal epithelium while in others they were round and oval and were growing in solid masses and in a pseudogland-like manner (Figs. 2 and 3). Invasion of the thin wall of the tube,

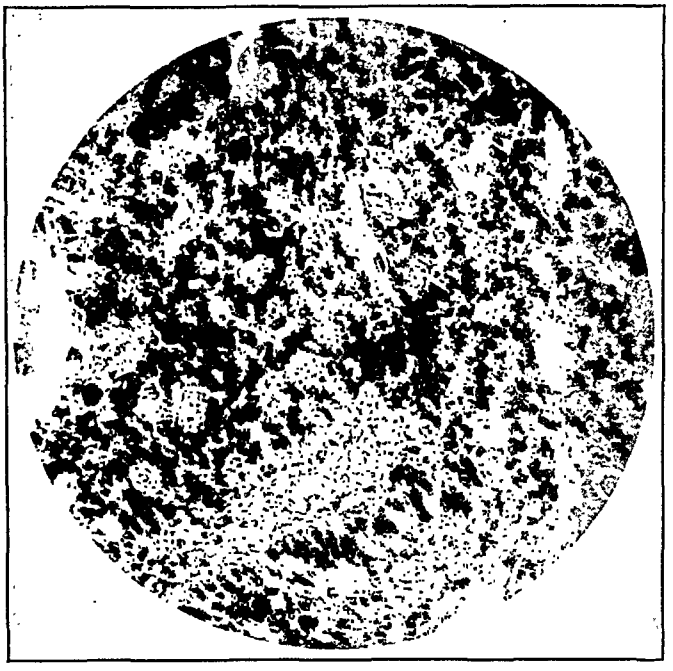


Fig. 3.—Case 1. High power microphotograph of Fig. 2, showing variation in size of cells, complete loss of polarity and mitotic figures.

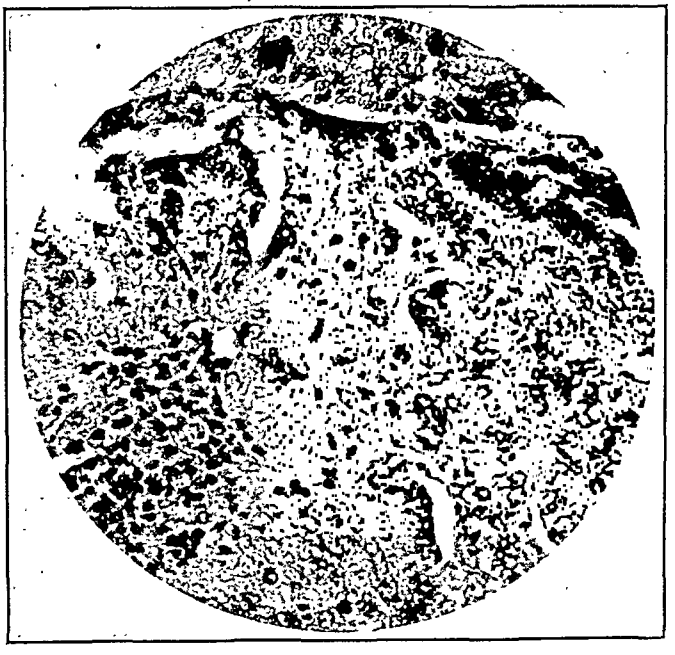


Fig. 4.—Case 1. High power microphotograph of secondary carcinoma of cervix.

by slender cords of malignant cells, had occurred. Throughout the central portion of the tumor multiple small areas of calcification were present. Mitotic figures were numerous and supporting stroma was very scant.

The cyst of the right ovary was lined by a single row of low cuboidal cells. The left ovary was atrophic.

Diagnosis.—Primary bilateral carcinoma of Fallopian tubes, myomas of uterus, cervical polypus, simple serous cyst of ovary (right).

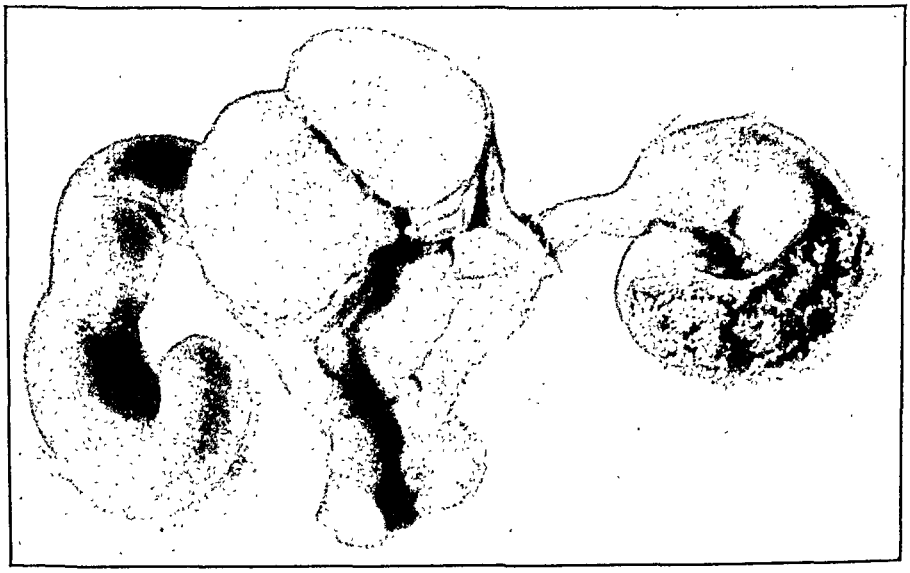


Fig. 5.—Drawing of gross specimen, Case 2, primary carcinoma of left tube.



Fig. 6.—Case 2. Very low power microphotograph, showing treelike pattern of tumor growth.

Patient did not return for observation as instructed until July, 1935, at which time she complained of loss of strength, and slight vaginal bleeding of seven months' duration. Examination revealed a large firm cervix, freely movable with a normal appearing vaginal aspect. The patient was examined under anesthesia. The pelvis was free from evident tumor masses, but on dilatation of the cervical os, the cervix was found almost completely replaced by tumor growth (Fig. 4) which had left an intact vaginal surface covered by normal appearing mucosa. Radium was inserted into the cervical canal and a dose of 4,000 mg. hours was given, followed

by a series of high voltage x-ray exposures to the pelvis. The patient remained well until March, 1937, when she began to lose weight and strength. In May she developed a persistent dry cough and x-rays of chest showed widespread secondary tumor. The patient died Sept. 7, 1937, four years after her original operation.

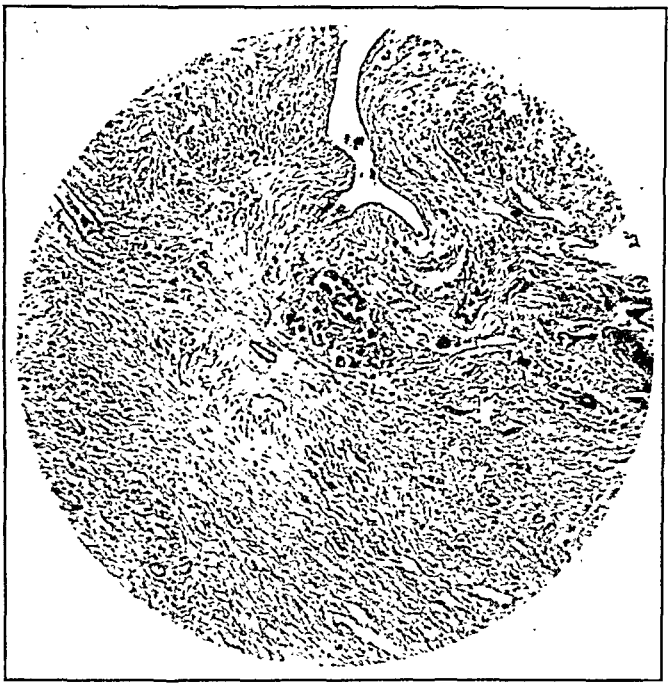


Fig. 7.—Case 2. Low power microphotograph, showing invasion of tubal wall close to serosa by malignant cells.

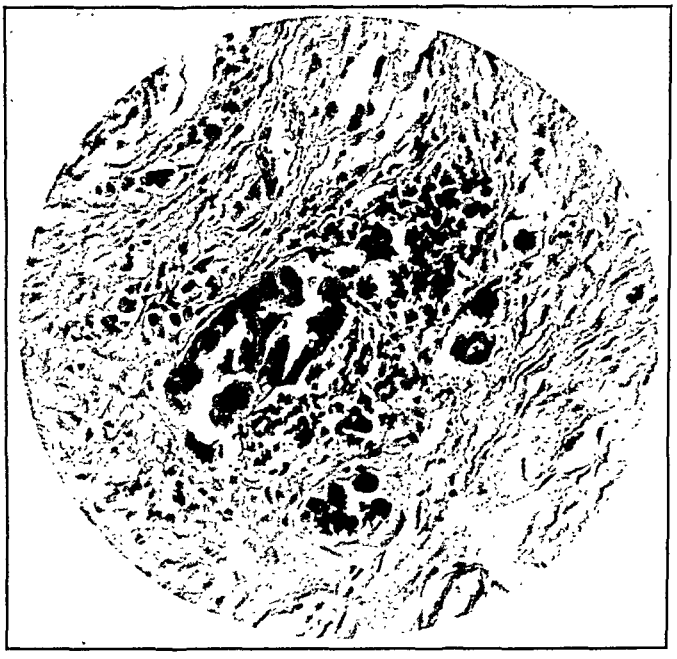


Fig. 8.—Case 2. High power microphotograph of invasion of wall of tube as shown in Fig. 7. Some cells appear to be in lymphatic spaces.

CASE 2.—Patient, aged 57 years, was admitted to the Toronto General Hospital in November, 1934. Her chief complaints were slight continuous vaginal bleeding and discharge for five weeks, general weakness for three months. Menopause had occurred ten years previously. Patient was married at 37 years of age and had never been pregnant.

Examination revealed a healthy-appearing female not acutely ill. Abdominal examination was negative. Pelvic examination revealed a nulliparous vaginal outlet and healthy small cervix. There was slight blood-stained discharge coming from cervical os. Uterus was enlarged, irregular, and freely movable. In the right fornix a soft tumor mass the size of a tangerine orange was palpable. It was not tender.

A preoperative diagnosis of ovarian neoplasm was made. Patient was examined under anesthesia and curettage revealed no evidence of carcinoma of the endometrium. The abdomen was opened and both tubes were found to be enlarged, closed, and retort-shaped. Numerous adhesions were present. Uterus contained a myoma in the fundus. Bilateral salpingo-oophorectomy and total hysterectomy were performed. Patient made an uneventful recovery from the operation and left the hospital fourteen days later.

Pathologic Report.—Specimen: Uterus, tubes, ovaries, and cervix (Fig. 5). Uterus and cervix measured 10 cm. in length. The fundus was occupied by a firm fibroid 4 cm. in diameter, and the cervix was small and atrophic. The endometrium was thin and partially curetted. The right tube was converted into a small retort-shaped hydrosalpinx 2.5 cm. in diameter. A few delicate adhesions were present. The left tube was narrow in isthmic portion but dilated in ampulla to a diameter of 3.5 cm. by a fine papillary growth. The lumen contained a small amount of blood-stained fluid.

Microscopic Report.—Uterus: Muscle bundles were atrophic and endometrium was senile.

Left Tube: Sections revealed the lumen filled with a fine papillary treelike growth of tubal mucosa (Fig. 6). The papillas were slender and covered by columnar and cuboidal epithelial cells. Variation in size, shape, and staining qualities was marked. The nuclei were hyperchromatic and mitotic figures were infrequent. Cells were irregular in arrangement, piled up several layers thick and in some areas seemed to be growing without evident supporting stroma. The tubal wall was deeply invaded by clumps of malignant cells (Figs. 7 and 8) some of which appeared to be lying in the lymphatic spaces. The right tubal wall was thin and atrophic, the plicae had disappeared and the epithelium was flattened.

The patient remained well until October, 1937, approximately three years after her operation. Beginning in October she noticed a gradual increase in the size of her abdomen. Examination revealed the abdomen markedly distended by free fluid (250 ounces at the last paracentesis) in which clumps of malignant cells were evident on section. Multiple small hard tumor nodules were palpable in the abdomen after paracentesis. X-ray of the chest showed no evidence of secondary carcinoma. The patient died in March, 1938.

DISCUSSION

These two cases of primary carcinoma of the Fallopian tubes are reported as rare and interesting gynecologic malignancies.

The clinical histories, progress of the disease, and gross specimens are similar in all major respects to the cases previously reported. In both specimens microscopic examination revealed fairly deep invasion of tubal wall and in one, malignant cells in lymphatic spaces. As in both cases the fimbriated ends of the tube were sealed off, it would appear that initial spread of the malignancy was by lymphatics or direct extension through the wall of the tube.

It seems highly probable from a review of the literature and a study of these two cases that previous tubal inflammatory disease is of some etiologic significance. The gross appearance of the tubes in these cases strongly suggests previous salpingitis. Both patients gave a history of a long period of sterility. The first case had symptoms of a mild post-partum pelvic inflammation after the birth of her only child. The second case had definite salpingitis in the tube, not the site of the malignancy.

The poor prognosis of carcinoma of the Fallopian tube is confirmed by the progress of these two cases. The probability of preoperative diagnosis is slight as there are no symptoms characteristic of malignancy in this site. The symptom, vaginal bleeding, is one common to carcinoma in most situations in female genital tract.

The operative treatment employed in the first case, supravaginal hysterectomy and bilateral salpingo-oophorectomy was obviously incomplete as within a year and a half, secondary carcinoma developed in the cervix. Despite the inadequacy of the operative treatment employed, this patient lived longer than the second patient. At the present time it would seem that bilateral salpingo-oophorectomy and total hysterectomy followed by high voltage x-ray therapy is the form of treatment that offers the best prognosis in this disease.

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170 St. George Street

PUERPERAL HEMORRHAGE IN CHIMPANZEES*

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In a recent descriptive account of pregnancy and parturition in a chimpanzee[1] brief mention was made of a slight hemorrhage occurring fifteen days after delivery. Subsequent observations of other individuals, the records of previous cases, and a few references to this phenomenon in the literature, indicate that it may be a typical characteristic of the early puerperium in chimpanzees. The observations may be of interest to gynecologists because they are unique. I have been unable to find any clinical reports of a similar nature.† The phenomenon also has not been reported for any other primates.

In his description of the first birth of a chimpanzee in captivity, Montané[3] (1915) states that sixteen days after birth there was a normal return of catamenia with an abundant flow for twenty-four hours. This bleeding may have been normal for a chimpanzee, but it certainly did not represent the return of catamenia. Following this no bleeding was observed for months. Undoubtedly it was of the same origin as the bleeding described in the present report. In a case (the birth of Cuba) observed by Senora Rosalía Abreu, but hitherto unreported, bleeding occurred twelve days after parturition. One other instance of puerperal bleeding of the type described herein is noted by Fox[2] in his account of a chimpanzee birth at the Philadelphia Zoological Gardens. The comment is brief: "Eleven days after delivery of our chimpanzee there was a bloody fluid seen once, about midday."

Post-partum hemorrhage within twenty-four hours is commonly observed and is easily accounted for. Our interest here is in bleeding which occurs, certainly as a direct consequence of, but several days following parturition. As a rule the total amount of the vaginal flow is not large and usually does not continue for more than forty-eight hours. Quantity

*The writer gratefully acknowledges the aid of the Committee for Research in Problems of Sex, National Research Council.

†Apparently it is not homologous to the true hemorrhage associated with endometritis post partum as described by Frankl. (*Frankl, Oskar:* Arch. f. Gynäk. 129: 87, 1926.)

and duration correspond, in most cases, to not more than a third of an average menstrual flow. In some cases it may be seen macroscopically for only a few hours and is easily overlooked unless frequent, careful search is made. The discharge is usually dark red, sometimes quite thin, and occasionally contains small blood clots.

Table I is a summary of the observations of puerperal hemorrhage made in these laboratories. For the purpose of comparison, the three cases observed elsewhere are also included. The table shows 16 out of 18 cases in which the phenomenon appeared on the ninth to sixteenth day after delivery.

The appearance of this bleeding has never been associated with any manifestation of pain or discomfort. It seems to be unrelated to age, parity, the general health or physiologic status of the individual. In short, the temporal relation to parturition is the only noteworthy characteristic, although it should be added that the length of gestational interval may be a determining condition. The bleeding was not observed in any of 13 early and late abortions.

TABLE I. PUERPERAL HEMORRHAGE IN CHIMPANZEES

CASE	NAME AND NO. OF ANIMAL	DATE OF PARTURITION	TIME OF BLEEDING (IN DAYS, POST-PARTUM)	REMARKS
1	Josie (30)	July 15, 1933	9, 10, 11, and 17	
2	Wendy (4)	Jan. 16, 1936	9	Premature (202 days*)
3	Nana (6)	May 2, 1934	10	
4	Mimi (44)	Oct. 15, 1936	10, 11 and 12	Premature stillbirth (167 days*)
5	Pati (42)	Mar. 27, 1937	10, 11, 12, and 13	
6	Pati (42)	May 14, 1933	11	
7	Soda (12)	May 5, 1937	11, 12, and 14	
8	Wendy (4)	Jan. 18, 1938	12	
9	Mona (36)	June 26, 1933	12	A twin birth
10	Mona (36)	June 26, 1936	15	
11	Josie (30)	Oct. 7, 1935	15, 16, and 21	An old blood clot or bit of placental tissue seen
12	Dita (40)	Apr. 13, 1937	15 and 16	
13	Nana (6)	Jan. 19, 1938	15 and 16	
14	May (32)	Nov. 10, 1937	18	Infant removed day after birth; no lactation
15	Cuba (46)	Apr. 11, 1935	20	Did not accept infant; no lactation
	Cucusa	Apr. 27, 1915	16 and 17	Observed in the Abreu primate colony, Havana, Cuba
	Mona	Mar. 24, 1926	12	Observed in the Abreu primate colony, Havana, Cuba
	Marianne	Oct. 1, 1928	11	Observed in the Philadelphia Zoological Garden
			Median time of appearance 12	

*Conception age.

It would be easier to account for this type of hemorrhage if histologic descriptions were available and if more were known of the process of involution of the uterus in chimpanzees. It seems probable that the bleed-

ing may coincide with an advanced stage of involution. In man the uterus undergoes a reduction of about two-thirds in size by the end of the second week of the puerperium. As the corpus resumes its normal size and again becomes a pelvic organ, expulsion of small quantities of blood and bits of retained placental or decidual tissue might be expected. Cases 14 and 15 add something to the validity of this explanation. It is well known that lactation facilitates the process of involution. The delay in appearance of the phenomenon in these two cases is associated with absence of lactation. In each case the infant was taken from its mother the day after birth.

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CONGENITAL TRANSVERSE SEPTUM OF THE VAGINA COMPLICATING PREGNANCY*

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A CONGENITAL transverse septum of the vagina is one of the rarer anomalies which may complicate pregnancy and cause dystocia. A review of the literature reveals a comparatively small number of cases. Brickner[1] in 1903, quoted Neugebauer[2] as having collected 56 cases from the literature in which cesarean section was performed, and 237 cases in which delivery was completed by various means through the vaginal route. Two hundred and seven of these cases were due to acquired atresia or stenosis of the vagina.

The remaining 86 cases could be attributed to congenital anomalies of the vagina and only a very small number of these cases had an anatomic description which resembled that of "transverse vaginal septum." Since 1895 there have been 37 true cases of congenital transverse septum described, 23 complicating pregnancy and 14 in the nongravid patient. I shall describe two additional cases of the congenital type. In both instances a careful history was taken to eliminate any such causative factors as inflammation or trauma of mechanical or chemical nature.

CASE 1.—(No. 87583.) M. M., a 27-year-old white female, was admitted to the Morrisania City Hospital on Feb. 22, 1937, because of vaginal bleeding. The patient gave the following history:

She could not recall having had any illness except measles and chicken pox, and the only previous surgical history was that of a tonsillectomy in 1934. The onset of her menstrual periods occurred at the age of twelve years, each period lasting four days and recurring regularly at intervals of twenty-eight days. During the first two days of her period, she had marked dysmenorrhea. There was no history of a previous vaginal discharge or vaginal trauma. She was married in April, 1936, and on questioning, it was found that she had experienced dyspareunia from the onset of her marital state to the present time. Her menstrual periods had been regular until July 16, 1936, and then she developed amenorrhea. After six to eight weeks she had mild morning nausea and occasional vomiting, and took for granted that she was pregnant. At about this time she noticed that there was a very slight amount of vaginal spotting which occurred almost daily, but never suf-

*Read at a meeting of the Section on Obstetrics and Gynecology, New York Academy of Medicine, May 25, 1937.

ficient to cause the patient alarm. This continued until February 21, when following coitus, she began to bleed vaginally, and passed a few small clots. She came to the hospital the following morning and was still bleeding very slightly.

The patient was a well-nourished white female who did not look acutely or chronically ill. Her color was good and she exhibited no signs of excessive blood loss. General physical examination was negative, except for the obstetric condition.

The uterus was enlarged to the size of a six and one-half months' gestation. There was no area of tenderness nor could any contractions be felt. A fetus with the vertex presenting was felt abdominally, and the fetal heart heard in the left lower quadrant.

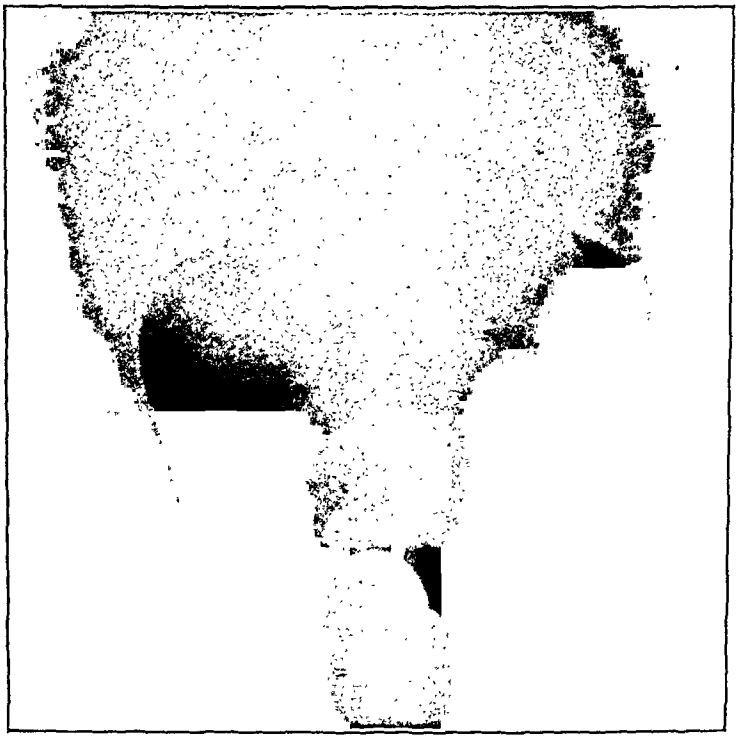


Fig. 1.—Anteroposterior view with lipiodal filling the cavity above the transverse septum.

A vaginal examination was deferred until the patient was typed and a blood donor available, in view of a possible placenta previa. The vaginal examination revealed normal external genitalia with remnants of a torn hymen. The introitus admitted two fingers and after passing into the vagina about 6 cm. the examining fingers impinged upon a smooth vault behind which a conical cervix could be felt. There was no narrowing of the vagina from its entrance to the vault.

A speculum was inserted and a transverse vaginal septum situated at about the junction of the middle and upper thirds of the vagina was visualized. There was a central orifice about ½ cm. in diameter. The margins of the orifice were eroded and bleeding. Pelvic measurements were normal. After a short period of hospitalization the vaginal bleeding ceased. The space behind the septum was distended with lipiodol, and an x-ray showed a space equal to about one-third the length of the vagina. The patient was referred to the prenatal clinic, and was again admitted to the hospital shortly before term. She went into labor on the evening of April 25. The vertex was fully engaged in the left occipitoposterior position. The patient had weak and irregular pains and the cervix was only 2½ fingers dilated at the end of twenty-four hours when her pains ceased completely. She had no pains during the following twenty-four hours, and the cervical dilatation remained stationary. Uterine contractions were renewed during the evening of April 27, and on the following morning

at 6 A.M., the cervix was fully dilated with the vertex impinging upon the septum. The orifice of the septum was now dilated sufficiently to admit a finger, and it was found that the septum was about ½ cm. in thickness at the edge of the orifice and increased to a thickness of 1½ cm. at its lateral attachments. The septum was incised at the areas of 8, 10, 2, and 4 o'clock, and Elliot forceps applied to the head which had rotated spontaneously to an anterior position and was low in the midpelvis. A living male infant weighing 8 pounds 12 ounces was delivered. The placenta and membranes were delivered intact by the Credé maneuver, and the vagina was then packed tightly with iodoform gauze to control bleeding. The total blood loss was approximately 350 c.c. The patient's condition was excellent and she required no further treatment. The packing was removed after twenty-four hours and there was no vaginal bleeding. The patient had an afebrile puerperium and vaginal examination on the tenth day revealed a vagina of normal depth and width without any constriction in the area of the pre-existing septum. The uterus was well involuted and the cervix had a small bilateral laceration. There was no evidence of any laceration of the vaginal walls and the only remains of the septum were a few small tabs, about ½ to 1 cm. in length. The patient was discharged in good condition.

CASE 2.—O. S., a 33-year-old negress, was referred from the prenatal clinic for study on March 3, 1937. On her first visit to the clinic it was discovered that she presented a vaginal anomaly. The patient gave the following history:

She had suffered from no illnesses except measles and occasional upper respiratory infections. The patient had the onset of her menstrual periods at the age of eleven years, having a three-day flow and an interval of twenty-eight days. Her periods were always regular and she experienced moderately severe dysmenorrhea during her entire period. There was no history of any inflammatory disease or vaginal discharge. The patient has been married fourteen years and has never used contraceptives, since she wanted to have a child. She always experienced slight dyspareunia. The patient had a regular menstrual period in October, 1936, and since then has had amenorrhea.

The patient was a well-developed healthy negress, and the general examination was negative, except for the obstetric and vaginal condition. The uterus was enlarged to the size of a five months' gestation and a small ballotable fetus was present. The external genitalia were normal and the remnants of a torn hymen were present. The introitus admitted two fingers easily which passed to a depth of 6 to 7 cm. when they impinged upon a smooth vaginal vault behind which a conical cervix could be felt. The vagina was broad and not constricted below this vault. A speculum was inserted and revealed a smooth membranous vault which appeared to have a median raphe with a small pin point opening in each half of the septum. A small probe could be passed through the left orifice but not through the right one. However, during x-ray studies with lipiodol, the fluid was seen to escape through the latter orifice. Because of this, the space could not be distended as well as in the previous case. X-rays, however, did show a good collection of lipiodol behind the septum.

The patient was again admitted to the hospital on July 10, 1937, with the history of the onset of labor at 8 P.M. July 9, with the membranes intact. Physical examination revealed a uterus of term size with a vertex presentation in the left occipitoposterior position and the head low in the midpelvis. The cervix was one finger dilated (rectal examination). After forty-three hours of active labor the cervix was fully dilated and the vertex low in the midpelvis still in the posterior position. Under general anesthesia, the septum was seized with two ring forceps and it split open radially in all directions, having become very thin during the progress of labor. A Scanzoni maneuver was employed to deliver a living infant, weighing 6 pounds 10 ounces. The total blood loss was approximately 350 c.c., and after the placenta and membranes were delivered intact, the vagina was packed with iodoform gauze. The packing was removed after twenty-four hours and there was no further bleeding. The patient had an afebrile puerperium and on discharge on

the tenth day the uterus was well involuted and only a few small tabs of mucous membrane could be found high up on the vaginal wall at the site of the former septum. There was no vaginal constriction.

The author wishes to express his appreciation to Dr. Harry Aranow, Director of the Division of Obstetrics and Gynecology, for his technical advice and assistance.

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EXTRA- AND INTRAUTERINE PREGNANCY

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THE coexistence of intrauterine and extrauterine pregnancy is sufficiently rare to justify the report of two additional cases.

CASE 1.—B. R., a 27-year-old married woman, was admitted to the Brooklyn Hospital Nov. 22, 1934, complaining of pain in the right lower quadrant of the abdomen of six days' duration and slight vaginal bleeding of three weeks' duration. The patient had missed one period four to five months previously (she did not remember which). The following three to four periods were normal as to time, duration, and amount of flow. The period due three weeks before admission began on time, but the flow continued with slightly more profuse bleeding the day of admission. Six days previously the patient first noticed a dull aching pain in the right lower abdominal quadrant. There was no radiation of the pain, but on sudden coughing or sneezing, the pain became sharp and stabbing. There had been no nausea or vomiting, no urinary symptoms and no leucorrhea. At the time the pain began the patient developed a coryza, followed by a cough.

The past personal history was negative except for a pregnancy eight years previously, which resulted in identical twins.

The admission temperature was 99.2° F., pulse 80, respirations 18, and blood pressure 118/65.

The positive physical findings were: (1) A few râles at the base of the right lung posteriorly. (2) Tenderness on deep palpation over McBurney's point, but no muscular spasm or mass. (3) On vaginal examination, a boggy uterus, enlarged to the size of an eight weeks' gestation, a hard but gaping cervix, not tender on motion, and some sensitivity but no mass, high in the right fornix. There was dark blood on the examining finger.

The blood count showed hemoglobin 67 per cent, red blood cells 3,250,000, white blood cells 11,400 with 87 per cent of polynuclears. The sedimentation time was over two hours. Urinalysis was negative.

The patient was given medication for her upper respiratory infection. The right lower quadrant pain disappeared, but the patient continued to spot. The white blood count at this time dropped to 10,000 with 80 per cent of polynuclears, and the sedimentation time was over three hours.

The patient was examined under avertin, gas, and oxygen anesthesia with findings the same as at the previous examination, except that a small, firm, movable mass was felt in the right adnexal region. The cervix dilated easily and the cavity of the uterus measured six inches. Portions of what appeared grossly to be placental tissue were removed from just inside the internal os, with an ovum forceps. Because of the size of the uterine cavity (which was larger than would be expected with an ectopic pregnancy), plus what appeared to be placental tissue, the patient was considered to have had an incomplete abortion, and a laparotomy was not done. The postoperative course was normal, but the patient continued to spot a very small amount of dark blood. She was discharged from the hospital six days postoperatively.

Pathologic report showed shaggy fragments of early placenta. Chorionic villi were present. Sections showed evidence of placenta.

The patient was seen at home four days after her discharge from the hospital because of vague lower abdominal discomfort and continued slight spotting. The blood pressure and pulse were normal, but she had had an evening rise of temperature to 99.2° F. Abdominal examination was negative. The pain subsided with rest in bed, but the evening elevation of temperature continued, associated with increasing constipation.

On the eleventh day at home the lower abdominal pain increased and the patient was unable to void. Her bowels had not moved in the preceding forty-eight hours. A vaginal examination, after catheterization, disclosed a tender, fluctuant mass, the size of an orange, in the culdesac.

The patient was readmitted to the hospital December 16. The temperature was 100.6° F., pulse 94, respirations 26, blood pressure 112/60. Blood count showed 3,000,000 red blood cells with 66 per cent hemoglobin and 16,640 white blood cells with 94 per cent polynuclears. The sedimentation time was twenty minutes.

A posterior colpotomy was performed and between three and four ounces of dark red blood were obtained. A culture of this blood was reported sterile.

The patient continued to spot and four days later she was discharging a small amount of bright red blood. A laparotomy performed the following day, disclosed a right-sided ruptured ectopic pregnancy. The broad ligament was edematous and the site of a considerable number of adhesions. A right salpingo-oophorectomy was done. A transfusion of 500 c.c. of whole blood was given postoperatively.

The convalescence was satisfactory and the patient was allowed home on the fifteenth day postoperative. At this time her hemoglobin was 75 per cent with 3,860,000 red blood cells.

Pathologic examination showed an ovoid mass 3.5 by 4.5 cm. in diameter. Part of an oviduct was recognizable along one margin of the mass. On section, it was red in the portions which had the appearance of an oviduct. The remainder was yellow, edematous, and had the appearance of an ovarian stroma.

Sections showed decidual reaction and chorionic villi in the dilated lumen of the oviduct. The villi were coarse and quite adult.

Diagnosis: Tubal pregnancy.

CASE 2.—E. R., aged 29 years, married four years, was admitted to the Queens General Hospital November 10, 1936, complaining of a constant sharp pain in the right lower quadrant of the abdomen. Her only pregnancy had terminated in the spontaneous delivery of a full-term child March 1, 1936. Her menses returned in April and were regular, every twenty-eight days, until September 2, the date of her last period. On October 10, she spotted for one hour. November 6 she was seized with sharp, nonradiating pain in the right lower quadrant which on November 10 was so severe that it caused her to faint. There was no nausea or vomiting, but there was slight dysuria. No shoulder pain, no dyschesia, and no vaginal bleeding or discharge.

On admission the general condition of the patient was very poor and she was in obvious shock. The abdomen was tender and rigid, with rebound phenomenon present in the right lower quadrant. There was no shifting dullness and no masses were palpable. Vaginal examination revealed no free bleeding and a uterus the size of an eight to ten weeks' gestation with a soft cervix which was exquisitely tender on motion. A tender doughy mass was present in the right fornix. A blood count at this time showed white blood cells 12,300 (85 per cent polynuclears), red blood cells 3,200,000, hemoglobin 62 per cent. The sedimentation time was thirty-five minutes.

A diagnosis of ruptured ectopic gestation was made and an immediate laparotomy performed. The peritoneal cavity contained about 500 c.c. of dark blood and blood clots. The uterus was soft and the size of a two months' pregnancy. The left tube and both ovaries appeared grossly normal. The right tube was the site of a ruptured ectopic gestation in the ampullary portion. A partial right salpingectomy was performed and the abdomen closed.

The patient was transfused postoperatively, her convalescence was uneventful and she was discharged November 20.

Pathologic Report.—Gross: Specimen consisted of a mass 4 by 5 cm. in diameter, an old blood clot being present near the fimbriated end. *Histologic:* Areas of decidual cells and chorionic villi were seen throughout the tubal mucosa.

Diagnosis: Tubal pregnancy.

On Feb. 2, 1937, the patient was readmitted to the gynecologic service for removal of a small but painful vaginal cyst. At that time the uterus was the size of a four and a half to five months' gestation, and fetal heart sounds were heard in the left lower quadrant. There had been no menses since Sept. 2, 1936. She was discharged Feb. 10, 1937. On May 27, 1937, the patient was admitted to the obstetric ward in active labor, and one hour later delivered a full-term living male weighing seven and a half pounds. The puerperium was uneventful and she was allowed home June 6, 1937.

SUMMARY

Two cases of extrauterine and intrauterine gestation are reported. In the first case, chorionic villi were found, both in the scrapings obtained from uterine curettage and in the tube which was subsequently removed at laparotomy. In the second instance, the intrauterine pregnancy went on to term, despite a laparotomy at the second month for a ruptured ectopic gestation.

I wish to express my appreciation to Dr. Arthur Antony and Dr. Harry P. Mencken for their permission to abstract these records.

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SUCCESSFUL TERMINATION OF PREGNANCY FOLLOWING BILATERAL SYMPATHECTOMY*

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THE treatment of essential hypertension until a few years ago was entirely medical. In 1923, Danielopolu, Bruening, and Stahl resected splanchnic nerves for this condition. In 1924, Pende proposed resection, and in 1934 Durante of Genoa proposed the same. Adson of the Mayo Clinic in 1925, performed a bilateral lumbar sympathetic ganglionectomy for essential hypertension. This was not successful, but the interest was again stimulated in 1930, after a successful rhizotomy. By October, 1935, twenty-seven patients were operated upon in the Mayo Clinic with different types of nerve resections for this condition. Several others reported a series of such cases as Crile, De Courcys, Page, Heuer, and Peet.

The conclusions of the Mayo Clinic from which the above data were obtained were that "the interval following the surgical procedure is too short to prognosticate what the ultimate results will be." They apparently feel quite hopeful that some form of surgery will eventually help a rather high percentage of well-selected cases.[1]

Among the patients operated upon at the Mayo Clinic only two have subsequently become pregnant. The first patient had previously borne three children, the youngest 6, and with none of the previous pregnancies had she shown signs of toxemia. Extensive sympathectomy was performed with relief of symptoms and reduction of blood pressure. Two years later she became pregnant. For two and a half months she was free from symptoms and her blood pressure was satisfactory. At three and a half months her blood pressure rose to 200/110. Termination was recommended. At five and a half months she was aborted by hysterotomy; her blood pressure was 200/110, and she was dyspneic and vomiting. Twelve weeks later her blood pressure was normal and has remained so for two years.[2]

*Presented at a meeting of the Worcester District of the Massachusetts Medical Society, April 13, 1938.

I wish to report a second case of pregnancy following an extensive sympathectomy.

Mrs. F., age 33 years, was referred to me by Dr. Brosnan of the Fallon Clinic of Worcester. At this time she had missed only one menstrual period, but a positive Aschheim-Zondek test had been obtained. The uterus was enlarged to about a two months' pregnancy. She gave the following menstrual history: began at 13, frequency every 30 days; duration one day; amount scant; no pain and regular every month. Her measurements in centimeters were intercristal 26; interspinous 20; external conjugate 19; bisischial -7, with a narrow arch; diagonal conjugate 13+, but an anteflexed, fused sacrococcygeal articulation. Her past history: diphtheria, chicken pox, whooping cough, mumps, and measles twice in childhood. Pneumonia at 8 and at 30; left nephrolithotomy at the age of 22 for renal stones; at 24 the same kidney was removed on account of infection; at 25 appendectomy; at 29 dilatation and curettage and hemorrhoidectomy; at 31 her blood pressure had gradually risen to 230/110, and she was classified as the essential hypertension type with no signs of damage in the remaining kidney; no evidence of arteriosclerosis or hypertensive heart disease. In 1935, at the Mayo Clinic an extensive bilateral subdiaphragmatic sympathectomy was performed. This included the section of both splanchnic nerves on each side as well as the two upper lumbar ganglia and partial resection of each suprarenal gland. She became pregnant two years later.

Course of the pregnancy: When she first came to me, at about two months, the blood pressure was 120/90 and with no symptoms of headache, faintness, or vertigo. I saw her every three weeks until the sixth month, and then every week until term. Her blood pressure ranged from 120/90 to 175/115. This maximum was reached at the seventh month and then receded to 140/95 at term. At no time did she have any toxic symptoms. Her weight increased from 128½ at the second month to 151 at term. At term her membranes ruptured before labor pains began. She had fourteen hours of first-stage labor and two hours of second-stage labor which was terminated with midforceps. The coccyx was fractured. A living female infant was delivered. She had an uneventful post-partum period. During labor the highest blood pressure was 184/118, and subsequently averaged around 150/110 while in the hospital. Five weeks after delivery her blood pressure was 160/90. Since then her blood pressure has reached as high as 170/105, but at present is 140/90. Although her weight is still around 140, she feels perfectly well and is enjoying the care of a normal healthy baby.

Only two cases of pregnancy following extensive sympathectomy have been reported, as far as I can determine. The first was aborted at five and a half months. The second case, discussed above, was carried through pregnancy to a successful termination. The first case proves that pregnancy following this operation is a definite hazard. The second proves that in spite of this hazard pregnancy can be carried through to a successful termination, but should be watched carefully throughout.

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27 Elm Street

Randall, Lawrence M., and Herrell, Wallace E.: Cystic Changes in the Endometrium, Surg. Gynec. Obst. 65: 666, 1937.

Microscopic study of 278 specimens of endometrium removed with a biopsy curette revealed that in 28 of them cystic changes had occurred. These tissues represented all phases of the menstrual cycle from the early proliferative phase to the late differentiation. The cystic change is believed to be the result of failure or deficiency of the function of the corpus luteum. The amount of proliferation is dependent on how complete or persistent this failure or deficiency has been.

Wm. C. Henske.

UTEROPLACENTAL APOPLEXY*

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UTEROPLACENTAL apoplexy is a grave complication of pregnancy in which there is marked hemorrhagic infiltration of the uterine wall with dissociation of the individual muscle fibers. The process may also extend to the broad ligaments and to the tubes and ovaries. The condition follows premature separation of the normally implanted placenta.

Couvelaire designates this condition as "uteroplacental apoplexy." Kolisko describes it as "hemorrhagic infarction of the uterus." Gibbon-Fitzgibbon terms it "ante-partum hemorrhage." Batizfalvy calls it, in mild cases of premature separation of the placenta, "ablatio placentae" and in severe cases, "uteroplacental apoplexy." This would seem to me to be a satisfactory nomenclature.

CASE 1.—Mrs. A. P., para vi, aged 35 years, American born, Italian parentage; of hypopituitary type; weight 210 pounds; height 5 feet 1 inch, admitted by ambulance, Jan. 21, 1937. Family and past personal histories negative. Menstruation began at the age of thirteen years; the periods were regular, every twenty-eight days, lasted four to five days, and were attended by no pain. She had had one abortion at three months, between the second and third pregnancies. Her five children were living and well. Patient stated that four of the labors were long and difficult. Last period July 21; expected confinement April 28, 1937.

Physical examination was negative except for the presence of dental caries involving several teeth, and edema of the feet which she said she had with each pregnancy.

On the evening of admission to the hospital, without any warning or any sign of pain, she had a profuse hemorrhage. She continued to flow intermittently after being put to rest with ice to her abdomen. When admitted to the hospital by ambulance the bleeding had ceased.

Examination revealed the uterus definitely larger than a 6 months' pregnancy, of firmer consistency than normal, with no pain or contraction. Inability to elicit the fetal heart tone was attributed to the obese abdominal wall. Rectal examination revealed the cervix to be about 1.5 cm. in length, patulous, 2 cm. The presenting part could not be palpated. The blood pressure was 130/70, the pulse 80, the temperature 98.6° F. The hemoglobin was 59 per cent. The patient's condition seemed satisfactory.

The patient and her husband were typed, with blood transfusion in mind, and each was found to be Type II. At this time the patient's pulse had increased to 104, the pressure dropped to 118/65, and the hemoglobin to 39 per cent. The red cell count was found to be 1,990,000, and the urine was found to contain a marked trace of albumin and occasional hyaline casts. The patient was given 400 c.c. of citrated blood by transfusion, following which she slept for three hours.

A vaginal examination was made, when it was found that the placental tissue could not be palpated through the patulous cervix. No fetal heart tone could be elicited. A definite ligneous consistency of the uterus had developed during the past three hours, and vaginal bleeding required change of pads four times since admission.

The diagnosis of ablatio placentae being established, the patient was prepared for laparotomy. Under nitrous oxide and ether anesthesia the abdominal cavity was entered through a suprasymphysial incision; the peritoneum was opened, exposing a uterus markedly injected, red and edematous with infiltration of blood in the uterine wall running at right angles to the axis of the uterus. The uterus seemed

*Read at a meeting of the Pittsburgh Obstetrical Society, June 6, 1938.

to exude serum, and there were several ounces of bloody fluid in the pelvic cavity. We felt that the involvement of the uterus necessitated its removal, and consequently a supracervical amputation of the uterus was performed without section, conserving both tubes and ovaries. The tissues were extremely friable, frequently necessitating duplicate ligatures and suture to control bleeding. The opening into the cervix was closed with inverting suture No. 1 plain catgut, the round ligaments were sutured to the stump of the cervix with No. 1 plain catgut, and the raw area peritonized with suture of the same material. Iodoform drain was enclosed in tissue in the lower angle of the wound extending down to the stump of the cervix, and the abdomen was closed in the same manner.

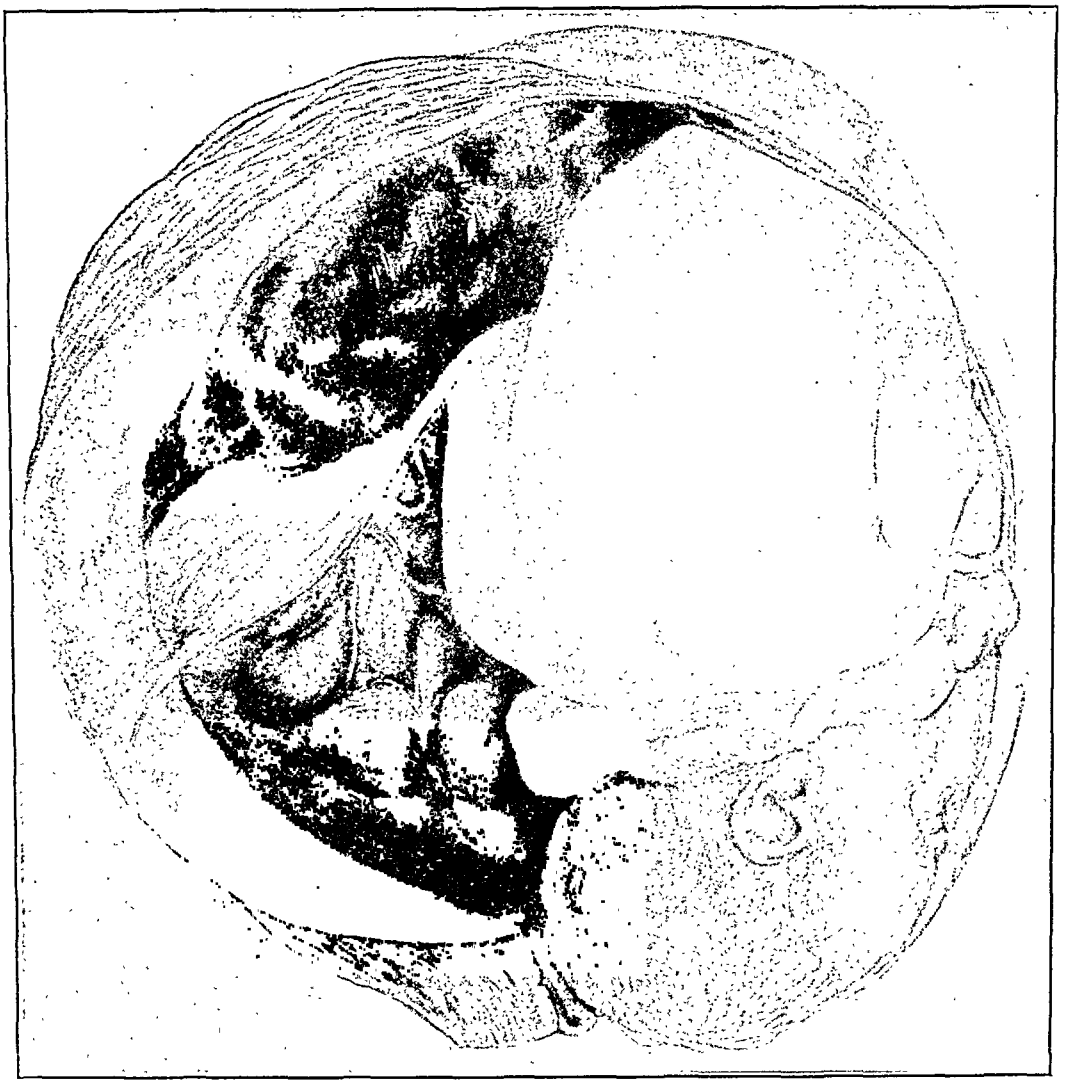


Fig. 1.—Drawing of Case 1, showing uteroplacental apoplexy occurring in upper pole combined with marginal insertion of the placenta.

The immediate postoperative condition was poor. A second transfusion and intravenous glucose proved of marked benefit. During the first four days the temperature went up to 102.2° F. and the pulse to 120; thereafter the patient made a good convalescence and was discharged from the Hospital at the end of nineteen days with slight drainage from the lower angle of the wound.

On opening the uterus there was found a low implantation of the placenta, but the hemorrhage had occurred at its upper pole, involving half its extent. The lower half of the placenta was not disturbed. The cord was shortened by a turn about the baby's neck and seemed to be under tension.

CASE 2.—Mrs. S., para i, aged 33 years, married two years. American born of Polish parentage; weight 159 pounds, height 5 feet 6 inches; admitted by automobile on the night of March 13, 1937. Family history negative. Her past personal history included heart disease at the age of 3 and a spinal injury by automobile accident at the age of 12. Menstruation began at the age of 18, and periods occurred at three-month intervals, lasting four days, moderate in amount with little pain. Last period July 5. There was quickening on November 22; estimated confinement date April 12.

Physical examination was negative. The patient had been observed prenatally on five occasions, and the blood pressure and urine were found to be normal. She developed edema of the ankles which at times was painful. After strapping this disappeared. Her weight increase up to two weeks prior to admission was 25 pounds.

On admission to the hospital the patient complained of abdominal pain which had started two hours earlier and localized over the uterus. The uterus was symmetrical in outline and tense on palpation. Repeated examination failed to elicit the fetal heart tone. Rectal examination showed the cervix about 1.5 cm. long, admitting the examining finger, and cephalic presentation was found.

The patient was given an HMC tablet No. 2 and slept at long intervals through the night. When awake she complained of backache. At 6 A.M. the following morning there was a show of blood, and by 9 A.M. there was a return of abdominal pain. The abdomen again became tense and the patient complained of continuous severe pain. The blood of the patient and of three relatives was typed and found to be Type II. The blood pressure was 114/70; red cell count 3,460,000; hemoglobin 65 per cent.

There was very little change in the cervix on rectal examination, and the patient was prepared for laparotomy.

The abdomen was entered through a suprasymphysial incision. The anterior aspect of the uterus was pallid and tense on palpation. It was opened in the midline, and a dead female fetus delivered by podalic extraction; weight 5½ pounds. The placenta, located high up on the posterior wall, was separated in about one-third of its extent; from behind the placenta, clots approximating a pint were removed. The uterus was delivered from the abdomen. The posterior uterine wall was edematous and infiltrated with blood. Hemorrhagic areas extended to the broad ligament attachment. Bleeding from the uterus was quite free with no tendency to contract after a second injection of pituitrin.

The uterus was amputated at the level of the internal os. The opening of the cervix was closed by an inverting suture, No. 1 plain catgut, and the vessels were ligated with the same material; the round ligaments were sutured into the stump of the cervix and the raw surface peritonized with No. 1 plain suture. The abdominal wound was closed in the usual manner. The postoperative condition was good and transfusion was omitted. The patient made an uneventful recovery and was discharged from the hospital at the end of twelve days.

I would like to thank Drs. Morris, Bruecken, and Rebbeck for technical help with these cases.

TUBERCULOSIS OF CERVIX

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JAMESON states that "Tuberculosis of the cervix is considered to be one of the more uncommon localizations of the disease in the female genital tract." Comyns Berkeley in 798 autopsies upon women who died of tuberculosis, found the reproductive tract involved in 62 cases, and of these, but 3 cases of tuberculosis of the cervix alone. Because of its rarity and the attendant problems involved in advising proper treatment in this type of case, the following case report is submitted:

R. I. (No. 81647), white, 19 years of age, Russian, housewife, was admitted to the private service of the senior author on Jan. 4, 1938, with chief complaint of vaginal bleeding occurring only after coitus. She had been married nine months and although staining was the usual aftermath following coitus in the early months of her marriage, this bleeding during the past four months had become markedly profuse. She had used no contraceptive measures and had been extremely anxious to become pregnant.

Her menstrual cycle, which began at the age of 12, at 26-day intervals and lasting three days, had always been of a normal rhythm. No dysmenorrhea, menorrhagia, or metrorrhagia was noted.

Both parents were living and well. Mother had goiter operation five years ago. Six sisters were living and well and all had had one or more children. Intensive questioning elicited no history of tuberculosis, diabetes, or cancer.

Except for tonsillectomy one year ago and measles as a child, patient had always been known as a "healthy" individual, and had no complaints concerning the respiratory, genitourinary, gastrointestinal, or cardiovascular systems.

(The husband of the patient was questioned as to family and personal history with negative results. Physical examination was essentially negative. Examination by a genitourinary specialist was reported as negative as to any possible source of tubercular or venereal infection in the male reproductive system.)

Physical examination of the patient revealed a well-nourished "healthy," white female with essentially negative objective physical findings except for those noted upon vaginal examination. The vulva was negative and presented a nulliparous introitus. Uterus was of normal size, anteverted and anteflexed, freely movable and regular. The fornices and cul-de-sac were negative. The cervix upon inspection appeared slightly hypertrophied, and, about the external os for a radius of about ½ inch, there was present a granular, velvety, angry red, and extremely friable erosion with a well demarcated and "punched out" regular margin. This area bled easily to the slightest touch. A preoperative diagnosis of a cervical erosion with tuberculosis, cancer, and syphilis to be ruled out was made, and trachelorrhaphy and microscopic study advised.

The blood pressure was 115/70; urine, negative; Rosenthal and Kahn, negative; guinea pig inoculation (catheterized specimen of urine), negative.

Blood examination showed hemoglobin, 13 gm.; R.B.C., 4,200,000; W.B.C., 10,000; polymorphonuclears, 81; and lymphocytes, 9.

X-ray Flat Plate of Chest—Summary: Old low grade Koch infection of apices especially the right one. Old hilus tuberculosis. Generalized peribronchitis and hypervascularization. No evidence of cavitation.

Frequent attempts to examine sputum for the tubercle bacilli were unsuccessful due to insufficient amount of expectorated material.

Vaginal, cervical, and urethral smears showed no gram-negative intracellular diplococci.

Under general anesthesia on Jan. 5, 1938, the cervix was coned out with the line of incision extending slightly beyond the demarcated edge of the eroded area. Post-

operative course was uneventful and the patient was discharged eleven days post-operative. Further studies in seeking other foci of tuberculous infection were incomplete, due to lack of cooperation upon the part of the patient who insisted upon leaving the hospital. She was seen two weeks after discharge, the suture line was well healed and the patient had no complaints.

Personal communication with the referring physician (Held) elicits the information that the patient no longer complains of bleeding after coitus, and, to all intents and purposes, feels well.

Pathologic Report.—(Laboratory No. 7358.) *Gross:* Specimen consisted of a conical shaped mass of tissue 1.7 cm. in height, 2.5 cm. in diameter. At the mucocutaneous junction, there was an angry red, granular zone which was completely circumferential. *Microscopic:* The mucosal epithelium was absent from over many



Fig. 1.—Tubercles showing caseation necrosis and Langhans giant cells beneath the surface epithelium.

areas. Exudate with polynuclear and mononuclear cells was adherent to the eroded surface. In the underlying tissue, conglomerations of mononuclear and polynuclear cells, with the former predominating, epithelioid cells and Langhans' giant cells were noted. Areas with necrosis and especially fibrosis formed the central portions of the cellular collections.

Examinations for acid-fast bacilli were negative.

Diagnosis.—Tuberculous endocervicitis.

DISCUSSION AND SUMMARY

It is not within the scope of this case report to discuss the mode of infection, prognosis or treatment of cases of tuberculosis of the cervix. Evaluating the facts in our own case, we were inclined toward a conservative type of therapy. It was primarily our intent to stress the importance of clinical observation and microscopic study in cases which ofttimes are dismissed as simple erosions of the cervix. Although it is estimated that about 75 per cent of the cases of tuberculosis of the cervix have involvement higher up in the genital tract, a case of a possible (since no laparotomy or curettage was performed) primary tuberculosis of the cervix is presented in an apparently healthy young woman.

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PREGNANCY COMPLICATED WITH BILATERAL CYSTIC OVARIES

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IN THE June issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, there appeared an article by Dr. Bernard Notes of Washington, D. C., relative to a bilateral oophorectomy done during the early months of a pregnancy, the pregnancy continuing on through to near term without interruption.

The following case I have to report is rather unique in the fact that the patient not only continued through to term, but two years later became pregnant from a very small stub of ovarian tissue and carried through to term again.

L. A. (Hospital No. 4017), white, aged 27 years, admitted to Orange General Hospital, Orlando, Fla., Oct. 29, 1935. The chief complaint on admittance was heavy, dull, dragging, constant pain in the left lower quadrant of the abdomen for the past two weeks. Past history other than the menstrual history was insignificant. Menstruation began at age of 14 years, regular every twenty-eight days, flow four to five days until after birth of first child, when occasionally she would skip one month. Pregnancies were as follows: Full-term normal delivery 1931 and 1935. One miscarriage at three months in 1934. Received six milk injections following this miscarriage. The second child born in 1935 was seven months old when the patient was admitted to the hospital, this child being breast fed. Patient stated that she had had only three periods since birth of child in April, 1935, the last period being Sept. 12, 1935, when she flowed three days, but since she was nursing her baby she was not alarmed over the irregularity of her periods.

The laboratory examinations were within normal limits and the Kahn test negative. Pelvic examination: Marital outlet with moderate relaxation of the perineum. Small amount of mucopurulent discharge. Cervix showed very slight erosion of the external os, but no laceration. Uterus was apparently not enlarged but was pushed to the left. There was a marked fullness in the left fornix which was soft, tender, and bulging. The right tube and ovary were not felt. A diagnosis of left cystic, ovary was made.

On Oct. 31, 1935, the patient was operated upon through a low midline incision under gas-oxygen-ether anesthesia. On opening the abdomen through a midline incision, the pelvis and culdesac were found to be completely and entirely filled with large bilateral cystic ovaries. The left ovarian cyst was the size of a large grapefruit and was contained entirely within the leaves of the left broad ligament. The right ovary was the size of a large orange, with apparent complete destruction of the ovarian substance. Both ovaries appeared to be nothing but large cystic sacs. The tubes were normal with the exception of a small cyst of Morgagni on the fimbria of the left tube. The uterus was soft and boggy and apparently two to two and one-half months' pregnant.

The operative technique was as follows: Dissection of the left intraligamentary cystic ovary intact, the leaves of the broad ligament being closed with No. 1 plain catgut. The right ovarian cyst was clamped and removed in the usual manner, the base being sutured with chromic catgut. The cyst was removed from the fimbria of the left tube and the appendix was not disturbed.

The specimen consisted of two large cystic masses, both intact and containing serous clear fluid. In the base of the right ovary, inside the cyst wall, was a large corpus luteum. Section of ovary showed large corpus luteum. No evidence of malignancy. Section of cyst wall showed many thin-walled venous sinuses and

considerable number of new fibroblasts. Lining of cyst was smooth. There was no evidence of malignancy. Diagnosis: Simple serous cystic ovaries, corpus luteum of pregnancy.

The postoperative course of this patient was entirely uneventful, and she was dismissed on Nov. 14, 1935, on her fifteenth postoperative day. At no time during her postoperative stay in the hospital did she receive any hormone therapy and received none during her prenatal period. She delivered a full-term, seven-and-three-quarter-pound baby on June 27, 1936.

This patient continued to have very irregular periods, at five- to eight-week intervals, after the birth of this baby, became pregnant again in 1937 and delivered a full-term baby on May 4, 1938.

There are two peculiar aspects of this case: First, the patient carried through to term after removal of the corpus luteum which was completely inclosed in the base of cystic ovary, and second, a subsequent pregnancy with only a very small stub of an ovary left.

NOTE: This patient presented symptoms referable to a complicated retroversion after her delivery in May, 1938, and was operated upon again on Aug. 10, 1938. A small piece of ovarian tissue was found at the site of the large intraligamentary cyst removed in 1935. This was completely subperitoneal and firmly bound down on the posterior surface of the left broad ligament, yet it was the source of another full-term pregnancy in 1938.

A REPORT OF A CASE OF INTRAUTERINE ASPHYXIA OF THE FETUS AT TERM DUE TO A TRUE KNOT IN THE CORD

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BROWNE, King, and others have reported cases of intrauterine asphyxia of the fetus due to a true knot in the cord and have suggested such cases be recorded in the literature. A report of one case is herewith submitted in which this complication caused the death of the fetus at term.

The occurrence of a true knot in the cord according to Williams is very frequent while Von Winckell estimates its occurrence as 0.4 to 0.5 per cent of all births. However, most writers consider death of the fetus, due to a true knot in the cord, as being of rare incidence and many authorities think that this condition is not possible. However, Browne has shown by experimentation that a knot in the cord can be sufficiently tight to occlude circulation of blood through the cord.

The patient, a white multipara, aged 29, para iv, presented herself to the Out-Patient Obstetrical Clinic for the first time on Oct. 1, 1937. The examination was negative with the exception of a mild cervicitis, second degree cystocele and rectocele. The Wassermann, Kahn and Kline tests were negative. The urinalysis was negative. The last menstrual period, which was normal, occurred on July 20, 1937, with expected date of confinement on Apr. 27, 1938. The patient did only the ordinary housework during the pregnancy. The ante-partum course was normal. There was a total weight gain of 23 pounds during the pregnancy. On Apr. 27, 1938, the estimated date of confinement, the McDonald measurement was 33 cm., head floating, fetal heart rate 136/min., rectal or vaginal examination was not made.

Upon abdominal examination on May 11, 1938, the McDonald was 34 cm., head entering the pelvis, fetal heart rate 132/min., L.O.A. position; there were active fetal movements. Ten hours later the patient noted the fetal movements were unusually active, but early the next day, May 12, she noted there were no further fetal movements. She returned to the clinic on May 14, at which time the McDonald was 34 cm., no fetal heart tones heard, no fetal movements perceived, and the head

on palpation seemed softer than normal. A clinical diagnosis of dead fetus was made. An x-ray examination of the abdomen showed no evidence of a dead fetus. On May 16, the patient went into labor and four hours later delivered spontaneously a dead macerated child. The umbilical cord was not entangled about the fetus. The cord measured 82 cm. in length; there was an average amount of amniotic fluid. There was a true tightly drawn knot in the cord at a point 54 cm. from the placenta. The cord from the knot to the placenta was a dark red due to hemorrhage and the blood vessels were thrombosed. For a distance of approximately 14 cm. from the knot toward the fetus the cord likewise was hemorrhagic with thrombosed vessels.

This evidence of a true tightly drawn knot in the cord was the basis for the diagnosis of intrauterine asphyxia with resultant death of the fetus at term.

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A SIMPLE AND INEXPENSIVE CARRIER FOR PREMATURE BABIES

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IT IS generally recognized that some form of heated carrier is desirable for transporting premature infants from the home to the hospital. In designing such a carrier for our Home Delivery Service three ends were sought: first, the heating system should be safe and simple to prepare; second, the size and weight of the carrier should be no greater than one person could easily transport; and third, the carrier should be inexpensive. The first objective was realized by using hot water bottles for providing the heat; the second by the choice of a black leather composition animal carrier which could be altered according to our special needs. The total cost of the carrier amounted to approximately eight dollars; the animal carrier cost four dollars, the three hot water bottles three dollars, and other materials not more than one dollar. This represents a considerable saving since a premature carrier of the type usually shown on the market costs from fifty to one hundred dollars.

The bag chosen was a light weight animal carrier which measured 10 inches deep, 11 inches wide, and 20 inches long. This type bag is easily transformed into a baby carrier as the lid is built like the roof of a house, thus giving an extra five inch clearance above the baby. It has a hole 7/8 inch in diameter at either end of the top as well as an opening 4½ by 5 inches at one end of the box part. The latter is protected by a wire netting over which a leather flap can be fastened. These openings provide for sufficient circulation of fresh air when the top is closed.

A wooden frame was built to fit inside the bag. This was designed to resemble a four-poster bed with the springs represented by a wooden floor raised 3 inches from the bottom of the bag to provide space for one hot water bottle. Holes ½ inch in diameter and 2½ inches apart were bored through the floor to permit the heat from the bottle to reach the baby. The four corner posts were connected to each other at the top by wooden bars. Over the bar on each long side a piece of soft woolen blanket was fastened and then redoubled on itself to form a pocket into which a hot water bottle could be inserted. These pockets were fixed in position by tacking the lower borders to the floor of the frame. The small ends of the frame were not lined. A premature jacket, a pad for the bed, and a small blanket completed the equipment. An opening 4¼ inches square was cut in the top of the carrier and an isinglass window inserted so that the baby can be under constant observation while being transferred to the hospital. Fig. 1 shows the bag.

Wishing to test the efficacy of the heating system the following experiment was conducted. The three hot water bottles were filled with water at 108°; the bag was opened in a room the temperature of which was 56°. A thermometer was placed in the bag, the bag closed and left in the room by an open window with cold air blowing on it. In fifteen minutes the temperature in the bag had risen to 76°.

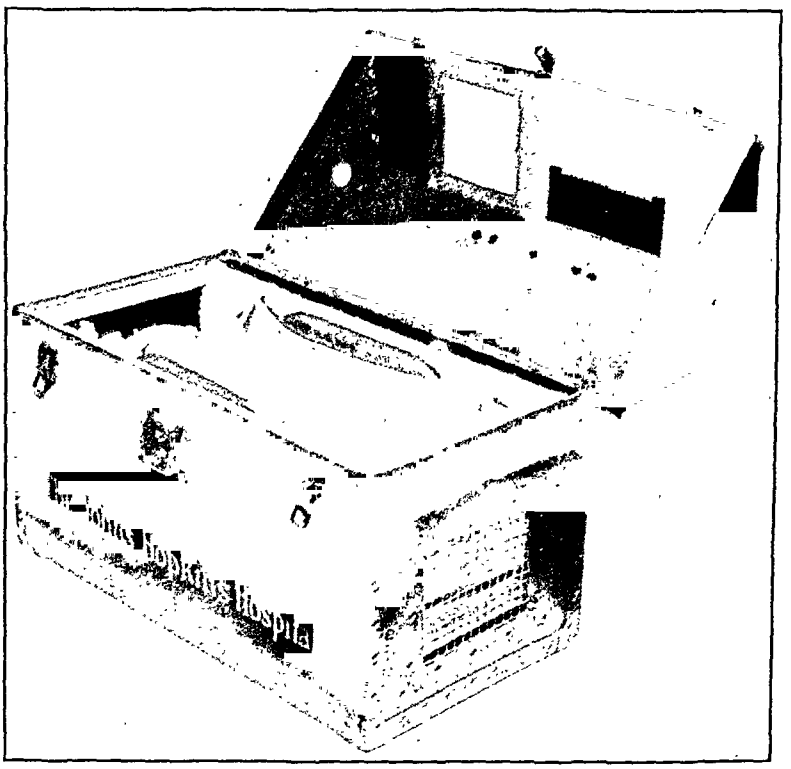


Fig. 1.

On transferring the bag to a warmer room of 78° the temperature rose to 85° within an hour, a greater length of time than the baby would remain in the bag. Therefore, the temperature at which the hot water bottles should be filled was set at not more than 110°. A thermometer was placed in the bag to be used for testing water in the home if necessary.

In our experience, this bag has proved a simple, inexpensive, and efficient means of maintaining the body temperature of premature infants while transporting them to the hospital.

Daniel, C., and Goldenberg-Bayler, S.: Vaccinotherapy in Metrorrhagic Adnexitis, Rev. franç. de gynéc. et d'obst. 33: 1, 1938.

Inflammatory adnexa are the cause of profuse uterine bleeding in 8 to 10 per cent of the cases. In the case of metrorrhagia where the customary treatment does not produce a cessation of the uterine bleeding, it is important to look for inflamed adnexa. The authors believe that vaccinotherapy is the treatment of choice. Not only is it superior to other forms of therapy, but it may be used as a diagnostic measure as well. Thus in a case where it is impossible to differentiate inflamed adnexa from an ectopic pregnancy, if the use of vaccinotherapy is followed by a diminution in size of the mass or even a cessation of the uterine bleeding, the mass is inflammatory and not a tubal pregnancy.

J. P. GREENHILL.

UMBILICAL CORD CLAMP

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AN UMBILICAL cord clamp is presented which may be easily sterilized and readily applied and removed. The constricting action of the clamp around the cord insures positive hemostasis regardless of changes in its size.

The clamp, which is illustrated in Fig. 1, is made of 3/16 inch tempered German silver and measures two inches in length. It comprises a spring loop carrying two spring arms. One spring arm is a single strand of wire, except at its free end where it is turned back upon itself to form a finger hold. The other spring arm comprises two parallel portions, between which the first mentioned arm moves. The spring arms

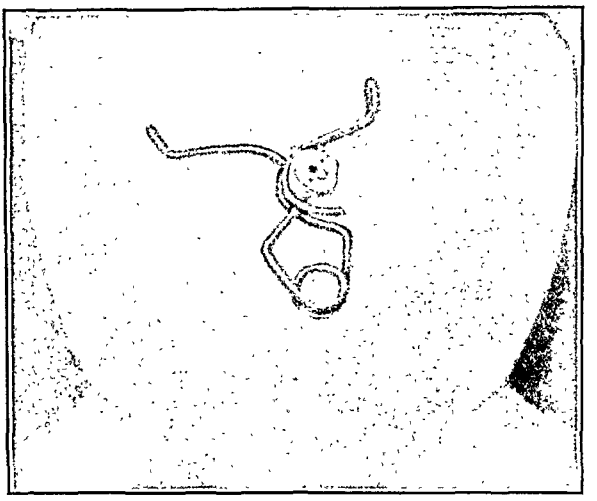


Fig. 1.

have opposing concave portions, which produce a constricting pressure on the entire circumference of the cord. The single strand spring arm tends to pull the cord into the space between the parallel portions of the other spring arm, which precludes the possibility of the clamp being accidentally pulled off.

The clamp is applied by approximating the free ends of the spring arms with the thumb and the index finger. The cord is then drawn through the circular opening formed by the concave portions of the spring arms. The cord is cut ½ inch distal to the clamp. The spring action of the clamp continues until the spring arms come to the position shown in Fig. 2. This insures adequate pressure on the cord even though there may be a decrease in the size of the cord due to the loss of Wharton's jelly.

After twelve to twenty-four hours the vessels are thrombosed and the cord dehydrated so that the clamp may be removed. Early removal of the clamp insures better healing of the umbilicus, because there is no possibility of traction on the cord and its premature separation.

HENRY FORD HOSPITAL

Editorial

Tuberculosis and Pregnancy

THE chance occurrence of pregnancy in a tuberculous woman is frequently looked upon as an unfortunate, if not dangerous, complication. The opinion still prevails among many physicians that abortion is essential to conserve the life of the patient. However, advancement in the treatment of pulmonary tuberculosis in particular has brought about a modification of this radical attitude and hopelessness need no longer prevail among women thus afflicted.

Of interest in this connection is a proposal presented at a recent meeting of the State Charities Aid Association of New York by Dr. Marian F. Loew, assistant director of the Division of Maternity, Infancy and Child Hygiene of the New York State Department of Health. After presenting evidence gleaned from a rather superficial review of the literature purporting to show the deleterious effects of pregnancy on the tuberculous woman, Dr. Loew outlined a plan being considered by the New York State Department of Health whereby an x-ray study would be made of every woman attending ante-partum consultations throughout the State, with a view of throwing "considerable light on the true incidence of tuberculosis in this group" and yielding "an estimate of administrative costs of including an x-ray as part of every ante-partum examination."

While the importance of recognizing a tuberculous lesion in a pregnant woman early in the course of gestation cannot be disputed, there are a number of points raised by Dr. Loew's proposal that are open to serious question. The evidence provided by a similar survey of 1,073 cases x-rayed by the Bellevue-Yorkville Health Demonstration in New York City in 1933 and 1934 and Bridgeman and Norwood's study of 14,000 patients at the Johns Hopkins Hospital, indicate that the incidence of tuberculosis in pregnancy approximates that of the population as a whole. This being so, as expensive a method of case finding as routine x-rays of the chest would seem to be unwarranted by a state health department even as a research problem. It should also be pointed out that the results of a study so conducted would fail to answer the question of the incidence of tuberculosis in pregnancy except as applied to the rather special low-income group of patients who would be seen in the State-conducted prenatal clinics.

In addition to these criticisms of the plan, Dr. Loew's proposal to defer the examination until the fifth month of pregnancy or even later "to secure a true picture of the lung findings" would do much to nullify the practical value of the study. It is now rather generally agreed that

if a gestation in a tuberculous woman is to be interrupted, the uterus should be emptied not later than the twelfth week, and if the pregnancy is to be allowed to continue, the patient should be well started on a tuberculosis regime by the fifth month.

Of much more practical importance than the proposed study would be efforts to provide adequate tuberculosis and obstetric care for pregnant patients with phthisis. At the present time facilities are almost entirely lacking, not only in New York State but also, with one or two exceptions, in other states as well for the care of the tuberculous gravid woman through the antenatal period, parturition, and puerperium. This being so, the deleterious effects of pregnancy on pulmonary tuberculosis must be attributed primarily to lack of proper treatment of the lung disease and secondarily, if at all, to the pregnancy itself.

Edwin M. Jameson, M.D.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

CESAREAN SECTION

AN ANALYSIS OF 1,000 CONSECUTIVE OPERATIONS

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(From the Department of Obstetrics and Gynecology, University of Chicago)

INCIDENCE

THE cases analyzed in this paper are 1,000 consecutive cesarean sections performed since the affiliation of the Chicago Lying-in Hospital with the University of Chicago, in the service of Dr. Fred L. Adair. The period covered by the study is from May, 1931, to March, 1938. There were 18,009 patients delivered in the hospital during this period, giving an incidence of cesarean sections among hospital cases of 5.5 per cent.

There were 50 operators for the entire series, 28 of whom were residents or full-time members of the departmental faculty and 22 were physicians in private practice. The departmental staff operated upon 79.2 per cent of the cases, the courtesy staff upon 20.8 per cent. No one man operated upon more than 8.2 per cent of the 1,000 cases.

Types of Operations.—

527	Laparotrachelotomies	52.7 per cent
399	Laparotrachelotomies and sterilization	39.9 per cent
59	Porro cesarean section	5.9 per cent
14	Classical cesarean section (7 sterilized)	1.4 per cent
1	Vaginal cesarean section	0.1 per cent

Sterilizations.—

465	of the patients were sterilized	46.5 per cent
	287 by Madlener technique	
	119 by resection of tubes (Adair technique)	
	59 by Porro cesarean section	

Maternal Mortality.—

There were a total of 8 deaths following the operations, a percentage of 0.8.

Two patients died of tuberculous meningitis, the operations being performed ante mortem to obtain a living child.

One patient, a decompensated cardiac case with chronic nephritis, died of cardiac failure following a classical cesarean section.

One death resulted from postoperative abdominal hemorrhage, from a bleeding omental vessel, the operation, a laparotrachelotomy, being performed because of a contracted pelvis and a previous cesarean section.

One death, 78 days postoperative, was the result of generalized infection; the patient had a history of chronic endocarditis. The laparotrachelotomy and sterilization was performed because of a mitral stenosis.

One death was from bilateral pulmonary embolism following thrombophlebitis. The laparotrachelotomy was done for placenta previa.

One patient died of generalized peritonitis following a Porro cesarean section performed after the membranes had been ruptured, the patient in labor over twenty hours. The indication was cephalopelvic disproportion.

One patient died of generalized peritonitis following a laparotrachelotomy combined with a myomectomy and left salpingo-oophorectomy. The indication for operation was fibromyomas of the uterus.

Morbidity.—The standard as advocated by the American Committee on Maternal Welfare was used in calculating the morbidity of these patients. Any patient with a temperature of 38° C.(100.4° F.) or over, recorded on any two days after the first twenty-four hours post partum, oral temperature readings being made at least four times daily, is regarded as febrile.

There were 438, or 43.8 per cent, of the 1,000 patients who became febrile according to the above standard and 122 who remained in the hospital longer than fourteen days postoperative. Of the 527 patients having a laparotrachelotomy without sterilization, 45.7 per cent became febrile. Of the 399 patients having a laparotrachelotomy and sterilization, 40.0 per cent became febrile. The lower morbidity in the sterilization group is probably explained by the fact that these operations are more frequently elective. Of the 59 patients having Porro cesarean sections, 59.5 per cent became febrile. Of the 14 patients having a classical cesarean section, 85.7 per cent became febrile. The one vaginal cesarean section was febrile.

Influence of Labor on Morbidity: Of the 1,000 patients, 334, or 33.4 per cent, were in labor at time of operation; 50.7 per cent of these patients became febrile. 173 patients were in labor twelve hours or more; 54.3 per cent became febrile. 161 patients were in labor less than twelve hours; 49.0 per cent became febrile. 666 patients were *not* in labor; 40.4 per cent became febrile.

Influence of Ruptured Membranes on Morbidity: Of the 1,000 patients, 207, or 20.7 per cent, had ruptured membranes at the time of operation; 113 or 54.6 per cent became febrile. 106 patients had ruptured membranes for twelve hours or more; 61 or 57.5 per cent became febrile. 101 patients had ruptured membranes for less than twelve hours; 53 or 52.5 per cent became febrile. 793 did *not* have ruptured membranes; 40.9 per cent became febrile.

Fetal Mortality.—There were 24 stillbirths, 17 of which were premature births (weighing less than 2,500 gm.). Abruptio placentae preceded 21 of these, placenta previa 2, and eclampsia 1. Forty-three infants, of which *27 were premature births,* died in the neonatal period. A total of 67, or 6.7 per cent, of the infants were stillborn or died in the neonatal period; 44 were premature and the majority of the deaths followed abruptio placentae or placenta previa.

Indications for Operation.—Many patients presented multiple indications for operations so that it was necessary to classify them according to the major factor in making the decision for operation in each case.

Disproportion and Dystocia: Contracted pelvis, 333; dystocia dystrophy syndrome, 41; cephalopelvic disproportion, 27; prolonged labor with inertia, 13; cervical dystocia, 21; Bandl's ring, 2; previous Dührssens incisions, 2; previous third tear recently repaired, 4; plastic repair of urethra, 1; atresia of vagina, 3; vaginal and vulval varices, 1; previous difficult labors with repeated stillbirths, 8; elderly primiparas, 7; fibromyomas of uterus, 13; transverse, brow or face, 7; 48.3 per cent.

Hemorrhage: Placenta previa, 79; abruptio placentae, 46; 12.5 per cent.

Toxemias and Related Conditions: Chronic nephritis, 42; pre-eclampsia (nonconvulsive), 65; eclampsia (convulsive), 9; essential hypertension, 7; 12.3 per cent.

Previous Cesarean Section: No other indication other than sterilization or threatened rupture of uterine scar, 118; 11.8 per cent.

Cardiac Disease: 104; 10.4 per cent.

Other Chronic Organic Disease and Certain Local Complications: Umbilical or ventral hernia, 9; diabetes, 9; pulmonary tuberculosis, 9; tuberculous meningitis, 2; tuberculosis of hip, 1; thrombocytopenic purpura, 2; twisted ovarian cyst, 2; right hydronephrosis, 2; 1 kidney, 1; Gaucher's disease, 1; other indication for sterilization, 4; carcinoma of cervix, 2; acute cholecystitis, 1; brain tumor, 1; multiple sclerosis, 1; 4.7 per cent.

Previous Cesarean Sections.—279, or 27.9 per cent, of the patients had a previous cesarean section. 233, or 23.3 per cent, had one; 42, or 4.2 per cent, had two, and 4, or 0.4 per cent, had three previous cesarean sections. Of the 279 patients who had previous cesarean sections, 207, or 74.9 per cent, were sterilized. 167, or 71.6 per cent, of the 233 patients who had one previous section, were sterilized. 37, or 88.1 per cent, of the 42 patients who had two previous sections, were sterilized. 4, or 100.0 per cent, of the 4 patients who had three previous sections, were sterilized.

Previous Stillbirths.—Of the 563 women who had previously borne children, 113, or 20.0 per cent, had had stillbirths. The majority of the previous stillbirths resulted from prolonged labors or difficult instrumental deliveries. The indication for the cesarean section in most of these cases was contracted pelvis, but in a few cases cesarean sections were performed because of the history of previous difficult deliveries with resultant stillbirths.

Period of Gestation.—9.9 per cent were from 41 to 44 weeks, 46.1 per cent were in the fortieth week, 36.4 per cent were 36 or more but less than 40 weeks, and 7.5 per cent were 26 or more but less than 36 weeks. The operations performed before the thirty-sixth week of gestation were almost entirely upon patients having abruptio placentae, placenta previa, chronic nephritis, or severe toxemia failing to respond to conservative treatment.

Anesthesia.—Local anesthesia alone, 610 cases, 61.0 per cent; local anesthesia and ethylene, 138 cases, 13.8 per cent; local anesthesia, ethylene and ether, 21 cases, 2.1 per cent; local anesthesia and avertin, 5 cases, 0.5 per cent; local anesthesia and cyclopropane, 4 cases, 0.4 per cent; ethylene, 98 cases, 9.8 per cent; ethylene and ether, 106 cases, 10.6 per cent; cyclopropane, 17 per cent, 1.7 per cent; ether, 1 case, 0.1 per cent.

The anesthetic of choice is novocaine, 0.5 per cent used for local infiltration. Ethylene is used to supplement the local anesthesia when necessary. Some patients in labor are difficult to control under local anesthesia and ethylene or cyclopropane is the initial anesthetic. Ether is only added when ethylene fails to relax the patient sufficiently.

SUMMARY

The comparison of the analysis of the first 500 operations with the second 500 operations shows certain significant differences.

The percentage of patients sterilized at time of operation increased 15 per cent. This increase is probably explained by the increased number of operations performed because of cardiac or other chronic organic diseases.

The use of the Madlener technique for sterilization increased 56 per cent while resection of the tube technique decreased 40 per cent.

The maternal mortality decreased 40 per cent (5 to 3).

The morbidity decreased 11 per cent.

The number of operations performed because of contracted pelvis decreased 33.2 per cent, for pre-eclampsia decreased 52 per cent, and for eclampsia decreased 85 per cent, while the operations performed because of previous cesarean section (no indication other than sterilization) increased 103 per cent, for cardiac disease increased 97 per cent, and for chronic nephritis an increase of 143 per cent.

Cesarean section is considered definitely contraindicated when a patient has a convulsive toxemia. Operations upon eclamptic patients are only performed when other indications for the operation are present and after the convulsions have been controlled by conservative treatment. There was only one operation performed on a patient with eclampsia in the second series of 500 operations. Cesarean section is performed on pre-eclamptic patients only when improvement has not occurred under conservative treatment.

The low mortality rate for these 1,000 operations has only been made possible by a combination of factors not readily available in smaller cities and rural areas. Most of the patients had attended the prenatal clinic throughout their pregnancies. Patients with cardiac disease, diabetes, tuberculosis, syphilis, toxemia, etc., are given special attention in designated clinics.

The hospital was built and equipped to provide every possible safeguard to the health of maternity patients. There is complete isolation of all infected mothers and infants from the other patients. Facilities are available for immediate transfusion of blood at any time.

Every patient in the hospital is seen by a senior staff obstetrician at least once a day and by the resident staff more frequently. No major operation is decided upon without consultation with the senior staff obstetrician and no operation is performed by a resident without assistance from a member of the departmental staff. Local anesthesia is the anesthetic of choice and without question the safest for this type of operation.

CONCLUSIONS

These cases have not been analyzed with the idea of minimizing the risk of cesarean section but rather to point out that when the operation is indicated, performed at the proper time, in a suitable hospital by a competent obstetrician, the mortality rate is consistently low. It is the ill-advised, ill-timed operations performed by unskilled obstetricians or surgeons in hospitals not equipped to safely care for maternity patients that have brought discredit upon the operation in many communities today.

Equally as good results are obtained in similarly organized and administered institutions and can be made possible in other hospitals. The requirements of the American College of Surgeons for approval of hospitals accepting obstetric patients should be rigidly met in every hospital.

Wilson, William: Treatment of Pruritus Vulvae by Alcohol Injections, J. A. M. A. 110: 493, 1938.

Forty-nine cases of pruritus vulvae which had been treated unsuccessfully by various conservative methods and were of long standing (average over eight years) were subjected to subcutaneous injections of 95 per cent alcohol. The needle is inserted perpendicularly through the skin. Only from 2 to 4 minims of alcohol is injected at a single insertion of the needle. The number and spacing of injections depend on the extent of the pruritus, the age of the patient, and the condition of the peripheral circulation. When the circulation seems unimpaired one may inject as much as 4 minims of alcohol beneath every square centimeter of the pruritic skin. General anesthesia was always employed.

Immediately after injection the labial folds, particularly the labia majora, become more or less edematous, reaching a maximum in from twelve to twenty-four hours. After twenty-four hours the edema slowly subsides, so that in from three to ten days the vulva usually appears normal, except for some induration.

The itching usually stops at once. If certain areas are overlooked or improperly treated, these can be reinjected under local anesthesia.

Few patients have complained of pain after alcohol injections. At first the swollen labia are slightly tender to firm pressure; this may persist until the swelling is gone. Some have been slightly annoyed by the numbness which naturally follows degeneration of nerves. Convalescence amounts to no more than a recovery from anesthesia. Some patients resumed their occupation after just one day.

Complications occurred in only two patients; small hematomas developed and were incised.

The results were as follows: 25 patients (51 per cent) had complete relief; 4 experienced partial relief; only 2 had no relief.

There have been 13 recurrences (26 per cent); 5 of these patients had a leucoplakic vulvitis.

GROVER LIESE.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MARCH 3, 1938

The following case report was presented:

Uncontrollable Postpartum Hemorrhage. Drs. J. H. Sharkey, J. B. Montgomery, and J. L. Richards.

The papers of the evening were as follows:

Post-partum Hemorrhage as a Cause of Death. Dr. C. T. Beecham. (For original article, see page 258.)

The Treatment of Myomata Uteri. Dr. J. P. Lewis.

Neonatal Mortality at the Philadelphia Lying-in Hospital. Dr. R. M. Tyson. (For original article, see page 241.)

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF JANUARY 22, 1938

The following papers were presented:

Endocrine Treatment for Sterility in the Female. Dr. E. W. Titus.

The Surgical Management of Uterine Prolapse and Associated Benign Pathology. Dr. E. H. Richardson.

MEETING OF MARCH 26, 1938

The following papers were presented:

Roentgen Diagnosis of Pregnancy. A Review. Drs. Joseph F. Elward and Joseph F. Belair.

Etiologic Factors in Sterility. Dr. J. Kotz and Dr. Elizabeth Parker. (For original article, see page 233.)

PITTSBURGH OBSTETRICAL SOCIETY

MEETING OF JUNE 6, 1938

The following case report was presented:

Uteroplacental Apoplexy. Dr. J. P. McComb. (For original article, see page 336.)

Paper of the evening:

An Evaluation of Obstetric Analgesics and Anesthetics. Dr. C. K. Murray.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Endocrinology

(Continued from January issue.)

Béclère, C.: Treatment of Postmenopausal Trophic Vulvar Disturbances, Bull. Soc. d'obst. et de gynéc. 26: 378, 1937.

For trophic vulvar disturbances such as atrophy, sclerosis, dryness, and pain Béclère recommends the use of ovarian hormones. He gives intramuscular injections of 10,000 units of estrogenic substance every fifteen days. This is continued until relief is obtained, then the injections are given once a month. In addition to this medication the patients are given local diathermy treatments, to improve pelvic and vulvar circulation and to intensify nutritional exchange. Further therapy consists of the local application of estrogenic substance to the affected vulvar tissue. This combination of therapy has given excellent and remarkably rapid results. The first symptoms which disappear are pain and dryness of the mucosa. Then the vulvar shrinking disappears and coitus again becomes possible. In the author's cases cure was obtained in two months.

J. P. GREENHILL.

Moricard, R.: Clinical Signs of Absence of Folliculin—Atrophy of the Labia Minora, Bull. Soc. d'obst. et de gynéc. 25: 526, 1936.

In women of menstruating age the labia minora are of variable size and they contain sebaceous glands. When follicular action disappears, there is a progressive decrease in size of the labia minora and a partial disappearance of the sebaceous glands. The labia then become glistening and smooth. Such a condition is observed a few months after castration. The retrogression of the labia minora may be asymmetrical. The author was able to restore the atrophic labia partially to their original state in one case by administering estrogenic hormone.

J. P. GREENHILL.

Palmer: The Schiller Test After the Menopause. Its Use in the Diagnosis of the Absence of Follicular Secretion, Bull. Soc. d'obst. et de gynéc. 26: 45, 1937.

The Schiller test depends upon the demonstration of the presence of glycogen in the squamous epithelium of the cervix by the addition of Lugol's solution. Palmer has used this test routinely during the past eighteen months, and he can confirm the claims made for the test, namely that glycogen is absent in carcinomatous cells. The present study was carried out on 42 women of whom 17 were in a spontaneous menopause, 19 in a menopause following operation and 6 in a menopause following radiation therapy. The author found that after the menopause glycogen disappeared from the squamous epithelium. In menopausal cases, staining with Lugol's solution produced a drab color in the areas free of glycogen. Conversely if Lugol's solution produces the normal dark discoloration more than three years after a hysterectomy or more than twelve years after a spontaneous menopause there is proved a persistence of follicular secretion. The cause for this persistence should be investigated.

J. P. GREENHILL.

Wiesbader, Jans, and Kurzrok, Raphael: The Menopause, Endocrinology 23: 38, 1938.

Two hundred patients were successfully treated for menopausal symptoms by means of estrogens, an ether-alcohol extract of the whole ovary, and calcium. The best results were obtained in patients in whom menstruation had ceased completely. Uterine bleeding (not menstruation) may result from such treatment. The significance of this is discussed.

J. THORNWELL WITHERSPOON.

Donald, H. R.: Treatment of the Female Climacteric by Follicular Hormone, Brit. M. J. 2: 899, 1937.

The climacteric is associated with a decline in secretory activity of the ovary, and a rise in gonadotropic secretion of the pituitary.

The duration of menopausal symptoms is subject to as much individual variation as their severity and origin. Mild menopausal psychoses—irritability, depression, loss of confidence and mental exhaustion—appear to be benefited by small doses of estrin (3,000 international units, or 0.3 mg. estrone by mouth daily). Vascular spasm with hypertension and edema also responds favorably to estrin therapy. The author employed intramuscular and oral doses temporarily, followed by oral administration alone for a longer period.

The wide range of rheumatic manifestations which characterize the climacteric may also have a vascular origin. Comparatively large amounts of estrin are required over a period of at least six months to benefit these patients. Visceral spasm and functional disturbances of the gastrointestinal tract respond to estrin therapy. No improvement was noted in cases of menopausal asthma and bronchitis. Low backache is difficult to relieve. Additional administration of corpus luteum may benefit the latter.

The dosage varies widely in individuals. Mild cases may require 1,000 international units three times daily by mouth to control symptoms. In severer cases 1 mg. estrone (10,000 I.U.) intramuscularly in oil twice weekly combined with 0.1 mg. (1,000 I.U.) three times daily by mouth may be necessary. Some required higher doses for an initial period of treatment. The vaginal smear test of Papanicolaou is an aid in deciding dosage. The duration of treatment varies in individuals. Reduction in dose must be effected gradually and over a long period of time, beginning at least two months after the patient has been symptom-free.

The question of cost is a vital factor to patient and hospital. It appears illogical for any hospital to deny its patients the established benefits of estrin therapy while permitting expenditure of equal sums of money in the care of many less sinister conditions. The ingenuity of the organic chemist may in the near future provide the answer to the cost problem.

F. L. ADAIR AND S. A. PEARL.

Israel, Leon S.: Evaluation of Endocrine Therapy in Primary Dysmenorrhea, J. A. M. A. 106: 1698, 1937.

Thirteen of the 39 patients were treated with estrogenic substance in the form of hydroxyestrin benzoate (Progynon-B) administered intramuscularly in doses of 5,000 to 10,000 rat units every fourth day for from three to four months. Of this group, six were entirely free from pain only while the substance was administered and four remained symptom free from two to four months following withdrawal of treatment. The remaining three patients were unaffected by the treatment.

Ten patients received antuitrin-S subcutaneously every other day in doses of 200 rat units (2 c.c.) for periods of from two to three months. Four patients experienced relief from dysmenorrhea: one has remained well for a period of fourteen months after the withdrawal of treatment, and the other 3 had painless periods during the course of the treatment only. The remaining 6 patients were unaffected by the treatment.

Sixteen patients were given small oral doses of estrogenic substance; 10 of these received emmenin in doses of 1 tablespoonful three times daily for periods averaging four months. Three of these were relieved of pain; one has remained symptom free for one year following the course of the treatment, and the other two only while emmenin was administered. The remaining 7 patients were unaffected. Six of the patients were given progynon tablets in doses of 600 rat units three times daily for periods averaging three months. Five of the 6 were unrelieved.

The results as a whole were disappointing.

GROVER LIESE.

Moffat, William: Treatment of Menstrual Migraine, J. A. M. A. 108: 612, 1937.

The result of treatment with gonadotropic urine extract in 17 cases of menstrual migraine, followed over a period of three years, was relief in all. Some, usually those who had suffered most severely over the longer periods of time, have been unable to discontinue treatment entirely.

In all but 4 of 11 cases studied, the sella turcica was found to be abnormal.

The following routine was evolved: Beginning with the fifth or seventh day after the onset of the menstrual flow a small dose, usually ranging from 2 to 6 rat units, is given; the dose is slightly increased daily until the tenth day, then rapidly increased, reaching a maximum of from 50 to 125 rat units on the fourteenth day, after which from 25 to 50 units are given daily until the onset of the next menstrual period.

The results tend to confirm the hypothesis that a leading factor in the production of menstrual migraine is an ovarian hypofunction, perhaps associated with an anterior pituitary hyperfunction.

GROVER LIESE.

Pasztor, M.: Ovarian Bronchial Asthma, Monatschr. f. Geburtsh. u. Gynäk. 105: 161, 1937.

It is the opinion of the author that bronchial asthma can be connected with the female genital organs in a causal relationship. The attacks of bronchial asthma which occur during pregnancy and at the time of the menses are most likely due to the vagotonic effect produced by the estrogenic hormones. The attacks of asthma which occur during the menopause are due to a hormonic disturbance the primary cause of which is absence of ovarian function. For the attacks which occur during the menses, corpus luteum preparations should be given to diminish the excessive activity of the estrogenic hormones. During the menopause on the other hand, ovarian extract should be administered.

J. P. GREENHILL

Schäfer, W.: The Influence of Estrogenic Hormone on the Reactions of Allergic Organisms, Med. Klin. 33: 1061, 1937.

Wiehler had observed that asthmatic women had an increase in their difficulties just before each menstrual period. Schäfer tried to determine the effect of ovarian preparations on the reactivity of sensitized female guinea pigs. He found that a much larger proportion of sensitized animals went into shock and died than not sensitized control animals. Hence an increased estrogen content in the body augmented the tendency to anaphylaxis in female animals. Schäfer warns physicians to give estrogenic substance to allergic patients only with great caution.

J. P. GREENHILL

Potter, Mabel F.: Oral Administration of Oestrin to Premature Babies, Brit. M. J. 1: 1201, 1937.

The author reports the use of progynon in 11 premature babies and 1 sick baby with satisfactory results. Given orally, this form of estrin appears definitely

helpful in premature infants. The babies cause less anxiety; the feedings are taken better; the initial loss of weight appears less and is usually made up sooner. No baby to whom it was given died.

The arguments in favor of this therapy, according to Martin (1929), are (1) that the blood of newly born babies at term contains a comparatively large amount of estrin; (2) this is rapidly excreted by the kidneys in the first three or four days of postnatal life; (3) a baby born prematurely is at a disadvantage because it lacks the stimulus of the estrin which would normally have been present in its blood had it remained in utero; (4) the administration of estrin helps to make up this deficiency.

F. L. ADAIR AND S. A. PEARL

Romaniello, Giovanni: The Action of the Hormones Contained in the Urine of Pregnant Women Upon the Mammary Glands of Animals, Folia Gynaec. 33: 2, 1936.

The author studied the action of the hormones in the urine of pregnant women upon anatomic development and function of the mammary glands of animals.

He found that the hormones affected the adult guinea pig mammary gland in such a manner as does pregnancy. In those already pregnant there occurred a relative hypertrophy; in those of puberty the glands approached the adult stage, as also did the mammary glands of castrated guinea pigs already in the stage of extreme atrophy.

MARIO A. CASTALLO

Engelhart, Erich: A New Action of the Lactation Hormone of the Pituitary and Its Effect on Ovary and Uterus, Klin. Wchnschr. 15: 425, 1936.

It is well established that the lactation hormone of the pituitary will, when injected into female guinea pigs, produce a definite activation of the breasts and actual milk secretion. Engelhart followed this reaction for eight days and then killed the animals in order to study the effect of this hormone on the ovary and the uterus.

He was unable to find any ruptured follicles or corpora lutea in the ovaries. There was in each instance a well-developed luteinization of the ovaries which was demonstrable grossly as well as microscopically. On serial sections of the ovaries, degenerated follicles were found but no corpora lutea, and the diffuse luteinization was found throughout the entire ovarian stroma.

The uterine mucosa showed a typical pregravid reaction and the myometrium failed to contract in response to pituitary extract in the normal manner. The author believes therefore, that it may be possible to explain the puerperal amenorrhea and sterility of lactation by these actions of the lactation hormone on the ovary and uterus.

RALPH A. REIS

Dott, Ugo Mugnai: Prehypophysis and Lacteal Secretion, Riv. ital. di ginec. 19: 505, 1936.

From a review of the literature relative to the production of mammary secretion and his own work the author draws the following conclusions: The hypophyseal gland, when stimulated by one hormone or another, responds with an increase of its own activity. The mammary glands respond to hypophyseal stimulation when they have been previously prepared by the ovarian hormones; however, they do not react in animals before puberty.

It would be very interesting, he states, to observe the lacteal secretion in adult hypophysectomized animals, treated with various other hormones.

AUGUST F. DARO

Mayor, José M.: The Inhibitory Effect of Follicular Hormone on Milk Secretion During the Puerperium, Zentralbl. f. Gynäk. 60: 2379, 1936.

Mayor summarizes the results of his observations by stating that the intramuscular injection of follicular hormone immediately following expulsion of the placenta exerts an inhibitory effect on the mammary glands of the puerperal woman.

Daily doses of 200 to 10,000 mouse units of follicular hormone, given over a period of six to eight days consecutively, do not show a clinically determinable inhibitory effect, whereas 250,000 mouse units of follicular hormone given in one dose produce a distinct inhibitory effect on the activity of the mammary gland.

Concerning the clinical application of these findings the author states that this form of therapy is being employed at his clinic in cases of stillbirths and abortions.

RICHARD E. SOMMA

Adrian, J.: Therapeutic Value of Injections of Folliculin in Cases of Undesired Secretion of Milk, Bull. Soc. d'obst. et de gynéc. 27: 331, 1938.

Research has demonstrated that estrogenic substances have a depressing action on the hypophysis and that the secretion of milk which depends upon the anterior pituitary hormone, prolactin, undergoes the same inhibition. He treated 100 women in whom it was desired to suppress the flow of milk by giving them a total of 60,000 units of estrin. This therapy brought about a reduction in the flow of milk only in 43 per cent of the cases. The preventive action of estrin was not encouraging.

J. P. GREENHILL

Ross, John R.: Prolactin—Its Effect on the Secretion of Woman's Milk, Endocrinology 22: 434, 1938.

Prolactin was administered, intramuscularly to mothers whose daily breast milk secretion on the fifth and sixth days was less than 400 c.c. The injections were given twice daily over a two-day period. One group of patients received a total of 400 U., whereas the second group received a total of 1,000 U. A control group of patients received intramuscular injections of normal saline.

The higher concentration of prolactin administered appeared to increase slightly the secretion of breast milk during the remainder of the stay in hospital. Of much more significance, however, was the fact that 7 out of 11 patients receiving this higher concentration of prolactin, whose records could be followed after discharge from the hospital, nursed their infants completely, whereas out of 8 such observed patients receiving the lower concentration of prolactin only 2 were able to nurse their infants completely. Of the 8 controls observed who received normal saline, only 1 nursed her infant completely.

Rather severe local reactions followed the injection of the larger amount of prolactin. It is probable that further purification of prolactin will eliminate these reactions. The administration of prolactin apparently has no effect on the fat, protein or ash content of the breast milk secreted. The effect obtained justifies further investigation. The urinary excretion of estrin in these cases was within the range found during the normal menstrual cycle.

J. THORNWELL WITHERSPOON

Dingemanse, Borchardt, and Laqueur: Male Hormones in Urine of Men and Women of Different Ages, Schweiz. med. Wchnschr. 67: 670, 1937.

They studied the amount of male hormone in the urine of men and women of different age groups. The male, like the female, hormones are eliminated in the urine in two different forms. The methods of determination formerly employed disclosed only the free form of the male hormone. However, a large

portion of the hormone is eliminated in the combined form. Thus the formerly detected quantities of 4 to 6 units of male hormone per liter of urine are much too low. By heating with acid, the hormone can be freed from the combination and thus becomes demonstrable. The authors summarize their observations: (1) The urine of healthy, sexually mature men contains 40 to 50 units. (2) The urine of healthy women contains approximately the same quantity of male hormone as does that of men (average, 30 to 60 units). (3) After sexual function has ceased, even during advanced senility and after castration, the urine still contains male sex hormone, but the quantities of the hormones are considerably less than in younger persons. (4) Boys and girls eliminate male hormone, but the quantities are smaller. (5) Pregnancy urine also contains male hormone. (6) It is improbable that the eliminated hormone originates in the ingested food.

J. P. GREENHILL

Korenchevsky: The Bisexual Properties and Co-operative Activity of Sexual Hormones and Their Effects on Females, Brit. M. J. 2: 896, 1937.

Bisexual properties have been found in nearly all the sexual hormones, and the cooperative activity of most of them with estrone and estradiol has been demonstrated on female rats experimentally. Suggestions are advanced as to the significance of these facts in regard to sexual physiology and pathology, and in relation to the therapy of general sexual disturbances in females. In the present state of knowledge, the author believes that the results of his experiments and those of other workers do not in any circumstances justify the use of the bisexual hormones with pronounced male activity in the treatment of diseases of women.

F. L. ADAIR AND S. A. PEARL

Groher, Hans: The Effect of Male Sex Hormone on Infantile Ovaries, Arch. f. Gynäk. 165: 347, 1938.

The authors found that male sex hormones will stop the development of normal follicles in the ovaries of immature females almost completely. These follicles developing before the administration of male sex hormones underwent degeneration and became atretic. In addition to this atresia of primary follicles there also resulted a marked inhibition of development of the secondary follicles.

RALPH A. REIS

Mocquot, P., and Moricard, R.: Action of the Male Hormone (Acetate of Testosterone) on Castration Symptoms of the Female, Bull. Soc. d'obst. et de gynéc. 25: 787, 1936.

The authors found that the administration of the acetate of testosterone modified and in general ameliorated the neurovegetative functional disorders which occur after castration in women. This substance, however, had no effect on the trophic vaginal disturbances secondary to castration. There may be a modification of the psychic state and in particular a sensation of euphoria and of increased activity but this effect is not constant. On the other hand there may result an increase in nervous instability.

J. P. GREENHILL

Zuckerman, S.: Inhibition of Menstruation and Ovulation by Means of Testosterone Propionate, Lancet 2: 676, 1937.

At this time it appears that any of the sex hormones will stop the estrous cycle. Estrin inhibits menstruation in monkeys and women, and so will progestin. This study is concerned with testosterone. One monkey which had had a reasonably regular menstrual cycle for 7 periods had a complete interruption of the cycle for 210 days when 25 mg. of testosterone were given twice weekly. A second monkey

had an amenorrhea of 122 days by the same treatment. Menstruation occurred eight days after discontinuation of the therapy. Detailed reports are given on the microscopic appearance of the ovaries.

Thus ovulation is suppressed in the normal mature monkey by estrin, and this study would indicate that temporary sterility could be secured and controlled by propionate testosterone. The masculinizing effects are slight and controllable. No changes occurred in the voice or hair growth, but the clitoris increased slightly. The internal reproductive organs remained uninjured, and menstruation was soon re-established with interruption of the therapy.

It is suggested that testosterone is worthy of clinical investigation to produce temporary sterility and to control uterine bleeding.

H. CLOSE HESSELTINE

Hartman, Carl G.: Menstruation Inhibiting Action of Testosterone, Proc. Soc. Exper. Biol. & Med. 37: 87, 1937.

Testosterone and testosterone propionate inhibit the onset of menstruation in the normally cyclic monkey, after castration and after cessation of estrin injections.

In this sense this androgen simulates the action of progestin, as it does also in its stimulation of mammary development and in its inhibiting action on the vaginal mucosa. In its effect on the sex skin, however, it seems able to replace the estrogens, for this remained brilliantly red in a castrate for sixty-three days after estrin deprivation.

HUGO EHRENFEST

Foss, George L.: Action of Testosterone Propionate on the Female, Lancet 1: 992, 1938.

In the opinion of the author metrorrhagia and menorrhagia can be controlled by the injection of testosterone propionate in adequate doses. In 16 cases a total dose of 300 to 800 mg. was required. In some of these, doses of 20 to 40 mg. given twice weekly for a few months were adequate, while in severe cases, dosages of 100 mg. daily or 150 to 200 mg. twice weekly were given. One patient failed to respond after a total dose of 2,800 mg.

A temporary therapeutic menopause with hot flushes may be induced with large doses so that menstruation is postponed for several months. Ovulation and luteinization are inhibited. The endometrium is in the resting stage. The breasts become smaller. There is definite increase in the size of the clitoris in some cases.

Before testosterone propionate can be regarded as a valuable addition to gynecologic practice its effects in large dosage over a long period of time must be studied.

CARL P. HUBER

Douay, E.: Some Uses of Testosterone Propionate in Gynecology, Compt. rend. Soc. franc. de Gynec. 8: 165, 1938.

Douay used testosterone propionate in women. The first successful results in women were obtained in cases of premenstrual congestion and pain of the breasts. Testosterone produces a rapid diminution in the congestion of the breasts after administration of 5 mg. every two days beginning ten to twelve days before onset of the menses.

The author points out that testosterone is an antagonist to estrin. After three or four injections are given not only do the breasts diminish in size but the other signs of hyperestrinism disappear. Thus the abdomen becomes softer and smaller and the cervical discharge diminishes. The menses often occur on time or perhaps even somewhat early.

Injections are necessary still during the second month and the third month but only one injection may be necessary to produce the desired result.

In cases of menopausal disturbances the author advocates the combined use of estrin and testosterone.

J. P. GREENHILL

Novak, J., and Wallis, O.: Masculinization Followed by Re-Femininization, Arch. f. Gynäk. 164: 543, 1937.

The authors describe the appearance of very marked and definite masculinizing symptoms and findings together with amenorrhea in a 32-year-old patient which were the result of a masculinizing tumor of the right ovary. This tumor was the size of a fist and grossly resembled a large corpus luteum on cross section. Microscopically the tumor is a typical luteoma rather than a tumor arising from misplaced suprarenal cortical cells because of the large lipoid contents of the individual cells. Removal of the tumor was followed by re-establishment of a normal menstrual cycle, a raise in the voice pitch, return of feminine contour and loss of most of the hirsutism which had developed. A résumé of the literature is included.

RALPH A. REIS

Glaser, E., and Haempel, O.: Hormonal Studies in a Case of Masculinizing Tumor of the Ovary, Klin. Wchnschr. 16: 859, 1937.

The authors report their findings in a case of a 27-year-old woman with a masculinizing tumor of the ovary. The tumor had been present for approximately nine months and had produced typical masculinizing symptoms. The tumor was removed and no metastases were found. It proved to be a partially degenerated fibroma of the ovary, with only certain characteristics of the typical arrhenoblastoma. These findings were confirmed by the presence of relative large amounts of the female sex hormone in the blood serum. At the same time, large quantities of the masculinizing hormone were found in the blood stream, even though the tumor itself yielded comparatively small quantities. In contrast to this latter, much larger quantities of the masculinizing hormone were found in the cyst fluid from a cyst of the opposite ovary. The authors recommend the early estimation of the hormone content of the blood serum in all suspected cases of masculinizing tumors.

RALPH A. REIS

Lepper, E. H., Pratt, C. L. G., Pratt, F. B., and Vaux, D. M.: Hormone Content of Ovarian Tumours, Lancet 1: 249, 1938.

The concentration of estrin was determined in 8 follicular cysts associated with typical hyperplasia of the endometrium. It was found to be present in approximately the same degree as in the ripe follicle but due to the larger amounts of fluid present the absolute amount of estrin in the ovary was considerably increased.

A total of 70 ovarian tumors and pre-operation urine specimens were examined for prolan A and B and for estrin. Prolan A was found in larger amounts in cyst fluid and urine in malignant tumors than in benign ones but was found in all types of the benign group. Prolan B was found in the cyst fluid of 2 out of 3 pregnant patients. Estrin was found in all follicular cysts. It was also present in the fluid from 2 of 11 germinal cysts but in very low concentration.

CARL P. HUBER

Kriss, B.: Feminizing Action of Male Sex Hormones, Monatschr. f. Geburtsh. u. Gynäk. 106: 157, 1937.

The author found that a lipoid male sex hormone derived from bull's testicles produced typical estrus changes in the vaginas of castrated female white mice. The same type of estrus changes were also produced by using a watery solution of androsterone. The author treated 48 women who had hypohormonal amenorrhea by means of male sex hormone and he observed good results in 50 per cent of the cases. The menses returned and continued after cessation of the treatment.

J. P. GREENHILL

Fels, Erich: Progesteron and the Male Genital Tract, Arch. f. Gynäk. 160: 461, 1936.

Fels carried out a series of animal experiments to determine the effect of progesterone on the male genital tract of animals. It is well known that estrin has a definite effect on the male genital tract. He was unable to find any changes ascribable to the progesterone either in an antagonistic or in a synergistic way. Such changes can only be produced by estrin.

RALPH A. REIS

Friedlander, E., and Moses, E.: Secondary Pregnancy Reactions in Chorio-Epithelioma of the Male, Wien. klin. Wchnschr. 22: 684, 1936.

The occurrence of chorioepithelioma in men has been reported in about 130 cases. Heidrich, Fels and Mathias found the anterior pituitary hormone in the urine in larger quantities with this tumor than in pregnancy. B. Zondek also found A. P. R. I-III reactions in three cases of malignant tumors of the testicle. In one case, hydrocele fluid also gave a positive reaction. These authors report a case of chorioepithelioma in a man 36 years of age. The symptoms were hemoptysis, loss of weight, and enlargement of the breasts. There were metastases to the lungs and retroperitoneal lymph glands. The patient died and the gross and histologic findings were verified. The testicular tumor contained in addition to a chorioepithelioma a seminoma, an epithelioma, and an epidermoid cyst. The hormonal influences of this tumor produced a gynecomasty with similar pregnancy changes and typical pregnancy changes in the hypophysis.

W. B. SERBIN

Item

American Board of Obstetrics and Gynecology

The general oral, clinical and pathological examinations for all candidates, Part II Examinations (Groups A and B), will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for reexamination in Part II must request such reexamination by writing the Secretary's Office before April 1, 1939. Candidates who are required to take reexaminations must do so before the expiration of three years from the date of their first examination.

Application for admission to Group A, May, 1939, examinations must be on file in the Secretary's Office by March 15, 1939.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Books Received

THE QUEEN CHARLOTTE'S TEXT-BOOK OF OBSTETRICS. By Members of the Clinical Staff of the Hospital. Fifth edition, with 4 colored plates and 293 text figures, 668 pages. J. & A. Churchill Ltd. London, 1938.

FUNDAMENTALS OF DENTISTRY IN MEDICINE AND PUBLIC HEALTH. By John Oppie McCall, Director of the Murry and Leonie Guggenheim Dental Clinic, New York, etc. 50 illustrations, 161 pages. The Macmillan Co., Inc., New York, 1938.

THE FUNDAMENTALS OF INTERNAL MEDICINE. By Wallace Mason Yater, Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine, etc. First edition, with 255 illustrations, 1021 pages. The Macmillan Company, Inc., New York, 1938.

CLINICAL LABORATORY METHODS AND DIAGNOSIS. A textbook of laboratory procedures with their interpretation. By R. B. H. Gradwohl, M.D., Director of the Gradwohl Laboratories, etc. Second edition, with 492 illustrations in the text and 44 color plates, 1607 pages. The C. V. Mosby Company, St. Louis, 1938.

THE PRACTICE OF MEDICINE. By Jonathan Campbell Meakins, M.D., Professor of Medicine and Director of the Department of Medicine, McGill University, etc. Second edition, with 521 illustrations including 43 in color. The C. V. Mosby Company, St. Louis, 1938.

CONTROL OF CONCEPTION. By Robert Latou Dickinson, M.D., Former Clinical Professor of Obstetrics and Gynecology, Long Island College Hospital, etc. A clinical medical manual with numerous original illustrations by the author. Second edition, 390 pages. Williams & Wilkins Company, Baltimore, 1938.

GEBURTSHILFLICHE UND GYNAEKOLOGISCHE THERAPIE, mit Einschluss der Heilmittel. Von Dr. Georg Burckhard, o. Professor der Geburtshilfe und Gynaekologie, Universitaet Wuerzburg. Zweite, umgearbeitete Auflage, 260 Seiten. Verlag von Ferdinand Enke, Stuttgart, 1938.

HANDBOOK ON CANCER, for the medical profession. The Authorship Committee, Department of Cancer Control, Canadian Medical Association, Toronto, 1938.

American Journal of Obstetrics and Gynecology

VOL. 37 MARCH, 1939 No. 3

Original Communications

THE HIPPURIC ACID EXCRETION TEST IN PREGNANCY

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(From Maternity Hospital, The University Hospitals, Cleveland, Ohio, The Florence Crittenton Home, Boston, Mass., and The Department of Obstetrics, Harvard University Medical School, Boston, Mass.)

IN A PRELIMINARY study[1] the determination of hippuric acid excretion after giving sodium benzoate by mouth, devised by Quick[2] as a test of liver function, was tried on a small series of normal and toxemic pregnant patients. A high percentage of subnormal values was obtained, and it was indicated that further investigation would be necessary to find, first, if the same results would hold in a larger series, and, second, were this so, if it might be possible to classify the cases with low hippuric acid outputs as to whether the cause lay in impaired production and/or conjugation of glycine with benzoic acid, or in impaired excretion of the formed hippuric acid because of renal dysfunction. Such was the purpose of the present study.

Since his original clinical paper Quick has published a series of additional cases studied by his method,[3] and several others have applied the test to some normal patients and to a number with potential or proved liver disease.[4-9] There were 5 toxemic pregnant patients in Kohlstaedt and Helmer's series on whom they obtained rather indeterminate results. There is general agreement that the test is practical and is a good index of parenchymal liver function, particularly when used repeatedly to follow the course of disease. It shows adequate correlation with other tests of liver function. It provides no specific index for distinguishing one type of pathology from another. Adlersberg and Minibeck object that the test does not differentiate between disturbed synthesis and disturbed absorption and/or excretion. It is my experience that significantly delayed absorption, as indicated by marked irregularities in the hourly excretion, is exceptional, but it may often be

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

an important question whether the conjugated benzoate finds its way through the kidneys at a normal rate. This is particularly pertinent when a condition that affects kidney function such as nephritis, hypertension, or pyelitis exists. Kohlstaedt and Helmer, and Fouts, Helmer, and Zerfas feel that by determining the urea clearance rate in combination with the hippuric acid test the problem of the kidney factor can be largely eliminated. While it is not unlikely that a correlation exists between the index of urea clearance and the rate of hippuric acid excretion, it remains subject to proof. In pregnancy, at least, where so wide a range of maximum and standard urea clearances is found in normal individuals,[10] the approach previously suggested[1] of determining the excretion of hippuric acid given intravenously appeared preferable.

In addition, since the detoxification and excretion of benzoic acid has been shown to depress the excretion of uric acid and to raise the blood uric acid level in nonpregnant individuals,[11] it seemed worth while to observe these phenomena in pregnancy.

MATERIAL

The subjects for this investigation were from two sources: a mixed group of multiparas and primigravidas from the dispensary service of Maternity Hospital, Cleveland, some of whom were delivered in the hospital, the rest at home, and a second group of young primigravidas housed from the latter part of pregnancy until after the puerperium at the Florence Crittenton Home, Boston. Random selection was made on the basis of normal physical examination and past history, negative Wassermann tests, and normal pregnancy to the time of testing. It was purposed to study normal pregnancy, but there were some patients who had minor evidences of toxemia overlooked at the time of testing or who later developed toxemia, and these are included as a separate group. No patient was considered normal if she had antepartum albuminuria or a blood pressure of 130/90 or greater, except that transient hypertension at the first visit or during labor was considered normal.

METHOD

Hippuric acid was determined by the modified gravimetric method of Quick.[2] Urine uric acid was determined by the method of Folin and Wu,[12] blood uric acid by the method of Benedict and Behre,[13] nonprotein nitrogen by the method of Folin and Wu,[14] and urea nitrogen by the method of Van Slyke and Cullen.[15]

The procedure previously described was followed.[1]

When urine uric acid was to be determined, the patient was instructed to void and note the time about one hour before she would arrive at the clinic. The bladder was then emptied before giving sodium benzoate and the time interval since the earlier urination calculated. After analysis of this specimen the uric acid excreted in the hour preceding the test could be roughly approximated. After the benzoate was given, aliquot samples for uric acid determination were taken from each hourly urine collection. The amount of hippuric acid thereby subtracted was later calculated and added to each hourly total.

When the excretion of hippuric acid after intravenous sodium hippurate was to be determined, it was found advisable to have the patients drink two glasses of water shortly before the injection in order to have ample specimens.

RESULTS

1. *Excretion of Hippuric Acid After 5.9 gm. of Sodium Benzoate by Mouth.*—Seventy-four tests were completed on 64 normal patients at various periods from the fourth to tenth lunar months of gestation. Twenty-three of these patients had repeated tests in or after the puerperium. In the tabulation 10 antepartum and 3 post-partum observations from the previous study are included. The results, together with other data, are shown in Table I. In order to compress the tables, the

TABLE I. NORMAL SERIES

CASE	AGE	GRAVIDA	GESTATION	HIPPURIC ACID OUTPUT AFTER SODIUM BENZOATE†			PER CENT EXCRETION OF I.V. HIPPURATE
				MAX. IN 1 HR.	TOTAL 4 HR.	PER CENT NORMAL	
1. G. L.	19	i	-132* - 18	1.02 1.04	3.08 3.45	102 115	
2. C. McM.	18	i	- 83	0.84	2.84	95	
3. M. G.	24	ii	- 41	0.54	1.32	44	
4. S. S.	19	i	- 65	0.73	2.15	72	
5. H. W.	28	iii	- 53	0.61	0.94	31	
6. M. H.	28	ii	-111 - 29	0.63 0.86	2.18 2.77	73 92	
7. M. D.	19	i	-181 - 41	0.83 0.86	2.58 2.47	86 82	
8. E. I.	24	i	-143	0.51	1.59	53	
9. J. Z.	16	i	- 8	0.61	1.93	64	
10. M. M.	20	i	-182 - 56	0.57 0.68	2.09 1.63	70 54	74.5
11. K. M.	25	iii	-136 - 10	0.86 1.03	2.24 3.40	75 113	
12. M. S.	26	ii	- 58	0.82	1.90	63	
13. E. K.	32	ii	-133	0.67	1.81	60	
14. H. S.	35	ii	-113	0.81	2.71	90	
15. F. T.	20	ii	-111 - 11 - 4	0.54 0.50	2.08 1.77	69 59	73.0
16. H. McM.	23	v	- 73	0.97	3.43	114	
17. D. W.	26	i	-141 - 36	1.01 1.07	3.69 3.78	123 126	
18. J. DeP.	22	i	-106 - 29	1.08 1.01	3.60 3.86	120 129	
19. S. Z.	22	i	-102 - 39	0.38 0.69	0.96 1.71	32 57	
20. L. W.	20	i	- 81	0.98	3.26	109	
21. M. M.	19	i	-121 - 37	0.96 0.93	3.29 2.91	106 97	
22. M. A.	21	iii	- 76	0.61	1.95	65	
23. J. K.	22	i	-123 - 46	0.75	2.52	84	77.5
24. P. G.	24	ii	- 99 - 67	0.77	2.83	94	82.5
25. H. S.	22	i	-131 - 66	0.84	2.95	98	86.5
26. S. Di. T.	23	ii	-150	0.98	3.38	113	
27. A. F.	23	i	-173 -155 -103	0.76 0.88	2.63 2.77	88 92	85.5
28. S. P.	23	i	-142	1.01	3.40	113	
29. A. Z.	22	i	-153	0.80	2.81	94	
30. W. A.	26	ii	-188	0.90	3.40	113	
31. F. E.	22	i	-150	0.72	2.67	89	

*—, Days before delivery; +, days after delivery.

†In grams of benzoic acid equivalent.

‡O. S., from earlier series.[1]

TABLE I—CONT'D

CASE	AGE	GRAVIDA	GESTATION	HIPPURIC ACID OUTPUT AFTER SODIUM BENZOATE†			PER CENT EXCRETION OF I.V. HIPPURATE
				MAX. IN 1 HR.	TOTAL 4 HR.	PER CENT NORMAL	
32. O. S.‡ 2	28	ii	-160	1.14	3.09	103	
33. O. S. 3	22	i	-162	0.99	2.64	88	
34. O. S. 5	21	i	- 1	0.88	2.32	77	
35. O. S. 6	32	i	- 76	0.75	2.26	75	
36. O. S. 10	27	i	- 89	0.96	3.37	112	
37. O. S. 11	26	i	- 36	0.90	2.95	98	
38. O. S. 16	20	i	-200	0.95	2.89	96	
39. M. B.	24	iv	- 78	0.81	3.02	101	
40. R. K.	19	i	- 88 - 86	0.97	3.07	102	81.5
41. E. R.	17	i	- 87 - 80	0.98	2.33	78	72.5
42. M. R.	30	i	- 73 - 71	0.74	2.65	88	76.0
43. H. G.	28	i	-106 -104	0.86	2.79	93	91.5
44. P. M.	15	i	- 60 - 58	0.90	3.26	109	81.5
45. O. S. 7	28	i	- 1 + 10	0.98 1.37	2.35 3.15	78 105	
46. O. S. 9	22	i	- 1 + 10	0.74 1.05	2.36 3.18	78 106	
47. O. S. 12	32	ii	- 8 + 11	1.00 1.03	2.45 2.93	82 98	
48. B. S.	30	i	-103 + 8	0.72 1.16	2.34 3.21	78 107	
49. E. P.	22	i	-155 + 9	0.83 1.32	2.03 3.61	68 120	
50. E. C.	20	i	-148 - 64 - 8 + 9	0.62 0.63 1.04	2.19 2.08 2.38	73 69 79	68.0
51. E. P.	17	i	-103 + 9	0.89 2.62	3.20 3.52	107 117	
52. R. O.	21	ii	- 35 + 8	0.55 0.82	1.59 1.94	53 65	
53. A. B.	20	i	- 83 + 11	0.80 1.09	2.01 2.99	67 100	
54. B. C.	23	i	-117 - 5 + 9	0.50 0.63 0.65	1.50 1.62 2.11	50 54 70	
55. L. R.	18	i	- 95 + 9	0.63 1.11	2.11 3.39	70 113	
56. E. B.	25	i	- 72 - 23 + 10	0.82 0.84 1.20	2.99 2.86 3.53	100 95 118	
57. A. G.	24	i	-102 + 9	0.70 1.10	2.07 2.87	69 96	
58. H. G.	25	i	- 85 + 9	0.73 1.02	2.46 2.61	82 87	

TABLE I—CONT'D

CASE	AGE	GRAVIDA	GESTATION	HIPPURIC ACID OUTPUT AFTER SODIUM BENZOATE†			PER CENT EXCRETION OF I.V. HIPPURATE
				MAX. IN 1 HR.	TOTAL 4 HR.	PER CENT NORMAL	
59. E. D.	18	i	- 43	0.96	2.87	96	
			- 41				85.0
			+ 30	1.19	3.38	113	
			+ 32				76.5
60. R. L.	16	i	- 38	0.86	2.88	96	
			- 36				77.0
			+ 45	1.11	3.41	114	
			+ 47				73.5
61. M. G.	25	i	- 36	0.60	2.09	70	
			- 34				72.5
			+ 48	1.11	4.11	137	
			+ 50				72.5
62. L. B.	20	i	- 22	1.09	3.20	107	
			- 20				74.5
			+ 55	1.26	4.02	134	
			+ 50				74.5
63. E. S.	16	i	- 63	0.90	2.90	97	
			- 61				90.5
			+ 41	0.96	2.89	96	
			+ 30				73.5
64. E. H.	23	i	- 39	0.84	2.63	88	
			- 37				58.0
			+ 31	1.19	4.06	135	
			+ 33				81.0
65. M. H.	26	i	- 65	0.99	2.92	97	
			- 63				89.0
			+ 19	1.12	4.03	134	
			+ 21				77.5
66. R. T.	16	i	- 58	0.77	2.41	80	
			- 55				72.5
			+ 18	1.00	3.65	122	
			+ 27				84.5
67. M. C.	26	i	- 50	0.67	1.80	60	
			- 48				49.5
			+ 20	0.95	3.39	113	
			+ 27				64.5
68. H. R.	29	i	- 3	0.53	1.79	60	
			- 1				81.0
			+ 46	0.80	2.99	100	
			+ 48				83.5
69. G. D.	17	i	- 3	0.70	2.42	81	
			- 1				78.5
			+ 32	0.98	3.56	119	
			+ 34				78.0
70. R. M.	17	i	- 16	0.82	2.64	88	
			- 14				82.5
			+ 19	1.00	3.56	118	
			+ 21				81.5

excretion for each of the four hours of the test has been omitted, but for each patient the maximum hourly output and the total for the four hours is given. As before, hippuric acid is represented as its gram-equivalent in benzoic acid, and the "percentage of normal" is calculated on the basis of 3 gm., being the average normal nonpregnant four-hour total.

There were 15 ante-partum tests on 13 toxemic patients with 3 repeated post partum. Eight ante-partum and 5 post-partum observations from the earlier series are included with this group. The results are shown in Table II. The toxemia in

most instances was minimal or undeveloped at the time of first testing. The cases have been roughly classified as "Early" or "Late" depending on whether or not evidences of toxemia appeared before the eighth lunar month, and as "mild" unless the blood pressure rose above 160/100 or there were pre-eclamptic symptoms, in either of which latter instances the designation was "severe." The above remarks also pertain to the toxemic group of Table IV.

About half of the patients experienced appreciable reactions of varying degree from the sodium benzoate. A typical reaction consisted of one or more of the following symptoms: flushing, headache, vertigo, tinnitus, and nausea. These effects occurred as often post as ante partum. Tests were interrupted by vomiting eight times. Emesis would probably have been more frequent had it not been possible to persuade other patients not to give in to their nausea. One patient (R. T., No. 61, Table I) who had no reaction at the first test ante partum, when given the benzoate post partum had rather prolonged symptoms and developed a rash and fever lasting two days. It was felt that the severity of the symptoms was contributed to by a mild mastitis, the premonitory signs of which she had failed to report before the test.

In considering the results of the 84 ante-partum sodium benzoate tests on normal patients, it is first to be noted that, while the observations are fairly well scattered through the last two trimesters, there are not enough of them to give valid indications of any progressive trend through pregnancy, which, indeed, could only be well established by repeated interval observations on the same patients from early pregnancy through the puerperium. Of the 14 patients who had repeated ante-partum tests, the division is about equal among those showing significant increase, decrease, or no change.

The average of the 84 observations is 2.57 gm. of hippuric acid as benzoic acid in four hours. This is 85 per cent of normal when compared to the average of 3 gm. in four hours accepted for normal nonpregnant individuals. The lower limit of normal is doubtless under 3 gm., and if we, arbitrarily, take 2.70 gm. as the lower limit of normal we find that but 37 or 42.8 per cent of the tests yielded outputs this great or greater.

The average output of the 26 post-partum determinations on normal patients was 3.22 gm. Of this group but 4, or 15.4 per cent, showed outputs of less than 2.70 gm.

Considering separately the normal patients who had both ante- and post-partum tests (Cases No. 45 to 70, Table I) we find that the ante-partum average of 29 observations on the 26 patients is 2.47 gm. Eight, or 30.8 per cent, excreted 2.70 gm. or more, while, as noted above, post partum, 84.6 per cent excreted 2.70 gm. or more. It should also be pointed out that even though the post-partum test may not in every case have yielded a "normal" value, in only one instance was the post-partum output not greater than the ante-partum output.

When the ante-partum hippuric acid outputs after sodium benzoate are plotted against the weights or surface areas of the patients for whom those figures are available, no correlation is shown, and it can be assumed that the magnitude of variation is greater than could be explained on the basis of individual variation in response due to size.

Before viewing the results of the benzoate tests on the toxemic patients, it should be repeated that this is not a representative toxemic group. Though the cases are too few for definitive analysis, they do show a lower average ante-partum hippuric acid output than the normal group, 2.41 gm., or 80 per cent, of normal, and only 5, or 21.7 per cent, had outputs of 2.70 gm. or better. The post-partum analyses are above the 2.70 gm. level in all but two instances and show increases in all but one.

It is usually considered that the normal individual should excrete at least 0.90 gm. of hippuric acid during at least one of the hours of the benzoate test. When all four-hour total and one-hour maximum excretions reported here are compared, a close correlation is shown between those with normal total outputs and with 0.90 gm. or more one-hour maximums, and between those with low four-hour total outputs and less than 0.90 gm. one-hour maximums. In any one case the hourly output

can be considered particularly significant only if the timing is accurate and the bladder completely emptied at each collection. Under the circumstances of this study it was not possible to control those factors absolutely.

II. *Excretion of Hippuric Acid After 2.0 gm. (2.26 gm. of Sodium Hippurate) Intravenously.*—Hippuric acid excretion as a result of this test was determined ante

TABLE II. TOXEMIC SERIES

CASE	AGE	GRAVIDA	GESTATION	HIPPURIC ACID OUTPUT AFTER SODIUM BENZOATE†			PER CENT EXCRETION OF I.V. HIPPURATE	CLASSIFICATION
				MAX. IN 1 HR.	TOTAL 4 HR.	PER CENT NORMAL		
1. A. K.	25	v	-135*	0.48	1.49	50		
			- 44	0.80	2.54	85		LM‡
2. D. R.	22	iii	- 48	1.03	2.53	84		LM
3. A. B.	19	i	- 29	0.84	2.25	75		LS
4. H. S.	26	i	-129	1.14	3.92	131		LM Wass. 4+
5. R. D.	32	iv	- 97	0.79	2.23	74		LS
			- 93				51.0	
6. P. S.	17	i	- 11	0.63	2.05	68		LM
7. L. B.	35	i	- 73	0.87	3.06	102		
			- 50				77.5	EM
8. W. F.	24	i	-162	0.73	2.65	88		EM
9. E. S.	19	i	- 6	0.78	2.56	85		
			- 7				73.0	LM
10. O. S.§17	29	ii	- 7	1.18	3.38	112		EM
11. O. S. 19	31	i	- 1	0.66	1.80	60		LM
12. O. S. 24	42	v	- 39	1.37	2.76	92		
			- 34				31.0	EM
13. O. S. 1	25	i	- 1	0.91	1.86	62		
			+ 11	1.01	3.13	104		EM
14. O. S. 13	23	i	- 1		2.27	76		
			+ 9	1.53	3.67	122		
			+ 8				79.0	EM
15. O. S. 14	30	i	- 1	0.75	2.04	68		
			+ 11		2.90	97		LM
16. O. S. 18	23	i	- 8	0.96	2.46	82		
			+ 10	1.09	3.54	115		LM
17. O. S. 21	29	i	- 1	0.82	2.59	86		
			+ 10	1.77	4.07	138		LM
18. M. P.	28	i	-101	0.89	2.52	84		
			- 6	0.83	2.80	93		
			+ 8	0.54	0.82	24		EM
19. C. P.	22	i	-128	0.54	1.85	62		
			+ 9	0.90	3.08	102		LM
20. E. B.	16	i	- 37	0.74	2.43	81		
			- 35				66.0	
			+ 53	1.10	3.95	132		
			+ 57				89.0	LM
21. M. C.	20	i	- 15	0.60	1.56	52		
			- 13				50.0	
			+ 20	0.73	2.65	88		
			+ 22				68.5	LS

*—, Days before delivery; +, days after delivery.
†In grams of benzoic acid equivalent.
‡E, early; L, late; M, mild; S, severe.
§O.S., from earlier series.[1]

TABLE III. NORMAL SERIES

CASE	AGE	GRAVIDA	GESTATION*	PER CENT EXCRETION HIPPURIC ACID AFTER INTRAVENOUS SODIUM HIPPURATE			
				30 MIN.	30-60 MIN.	60-120 MIN.	TOTAL FIRST HR.
1. M. Z.	35	iii	- 52	54.5	9.0	24.5	63.5
2. I. H.	21	i	-173	70.0	11.0		81.0
3. A. S.	25	ii	- 75	74.0	9.0		83.0
4. E. A.	19	i	- 73	60.0	15.5		75.5
5. E. C.	20	i	- 64	46.5	19.5	9.5	66.0
6. H. H.	23	i	-126	59.5	26.5	19.5	86.0
7. E. C.	28	i	- 90	68.0	14.5	8.5	82.5
8. M. D.	22	i	- 4	52.0	19.0	7.5	71.0
9. R. M.	32	ii	-134	80.0	15.0	6.0	95.0
10. J. K.	18	i	- 18	22.5	39.5	18.5	62.0
11. J. F.	38	iii	- 56	64.0	15.0	5.5	79.0
12. L. M.	37	iv	-126	31.0	38.5	13.5	69.5
13. C. R.	30	ii	-128	62.0	10.0	4.5	72.0
14. R. T.	22	i	-148	78.0	10.0	6.0	88.0
15. M. D'A.	21	i	- 48	54.5	19.0	15.0	63.5
16. M. T.	26	ii	- 34	69.0	16.0	12.5	85.0
17. C. D.	20	i	- 91	47.0	26.0	10.0	73.0
18. E. E.	18	i	- 83	81.0	9.5	3.5	90.5
19. E. A.	21	i	-109	73.0	14.5		87.5
20. F. T.	20	i	- 4	49.0	24.0		73.0
21. I. B.	25	ii	-157	60.0	14.0		74.0
22. J. P.	21	i	- 51	58.0	20.0	13.0	78.0
23. M. M.	20	i	- 56	56.0	18.5		74.5
24. H. H.	29	i	- 59	51.0	31.5	9.5	82.5
25. M. R.	28	v	-108	62.5	18.5	10.5	81.0
26. L. T.	35	vi	- 66	69.0	14.5	6.0	83.5
27. H. S.	32	i	- 68	46.0	40.5		86.5
28. P. G.	24	i	- 67	60.5	22.0		82.5
29. E. P.	37	i	- 55	62.0	21.0	11.5	83.0
30. E. V.	18	i	-165	73.0	18.0	8.0	91.0
31. A. O'B.	26	i	- 73	41.5	31.5	11.0	73.0
32. A. M.	21	i	-152	68.0	13.5	6.5	81.5

*—, Days before delivery; +, days after delivery.

TABLE III—CONT'D

CASE	AGE	GRAVIDA	GESTATION	PER CENT EXCRETION HIPPURIC ACID AFTER INTRAVENOUS SODIUM HIPPURATE			
				30 MIN.	30-60 MIN.	60-120 MIN.	TOTAL FIRST HR.
33. C. P.	34	vii	- 61	68.5	18.5	9.5	87.0
34. L. S.	21	i	-113	69.0	16.0	6.0	85.0
35. S. F.	24	iv	- 3	56.5	12.0		68.5
36. A. L.	20	i	-123	72.0	18.5	10.5	90.5
37. A. F.	23	i	-103	64.5	21.0		85.5
38. M. S.	27	ii	- 36	76.5	10.5		87.0
39. J. K.	22	i	- 46	47.5	30.0		77.5
40. R. K.	19	i	- 86	55.5	26.0		81.5
41. E. R.	17	i	- 87	36.0	36.5		72.5
42. M. R.	30	i	- 72	46.5	29.5		76.0
43. H. G.	28	i	-106	61.5	30.0		91.5
44. P. M.	15	i	- 62	65.5	16.0		81.5
45. E. F.	17	i	- 53 + 9	59.0 52.0	14.0 16.0	12.5 21.0	73.0 68.0
46. M. B.	26	i	- 46 + 9	50.5 43.0	33.0 20.5	9.0	83.5 63.5
47. E. D.	18	i	- 41 + 32	64.5 61.0	20.5 15.5		85.0 76.5
48. R. L.	16	i	- 36 + 47	40.0 57.0	33.0 16.5		73.0 73.5
49. M. G.	25	i	- 34 + 50	54.5 58.5	18.0 14.0		72.5 72.5
50. L. B.	20	i	- 20 + 50	55.5 59.0	19.0 15.5		74.5 74.5
51. E. S.	16	i	- 63 + 30	71.0 56.0	19.5 17.5		90.5 73.5
52. E. H.	23	i	- 37 + 32	41.5 61.0	16.5 20.0		58.0 81.0
53. M. H.	26	i	- 63 + 21	67.5 56.5	21.5 21.0		89.0 77.5
54. R. T.	16	i	- 55 + 27	21.5 62.0	51.0 22.0		72.5 84.0
55. M. C.	26	i	- 48 + 27	32.0 46.0	17.5 18.5		49.5 64.5
56. H. R.	29	i	- 1 + 48	69.0 66.5	12.0 17.0		81.0 83.5
57. G. D.	17	i	- 1 + 34	61.0 61.0	17.5 17.0		78.5 78.0
58. R. M.	17	i	- 74 + 21	63.5 63.0	19.0 18.5		82.5 81.5

partum on 58 normal patients at various stages of pregnancy, and post partum on 14 of these same patients. Twenty-one ante-partum observations on 19 toxemic patients were obtained, one being repeated post partum, and 4 ante- and 1 post-partum determinations from the earlier series are included. When the patients who were given sodium benzoate also had the intravenous hippurate test, the results of the latter, in the proper time relations, are included in Tables I and II. All of the observations from the intravenous tests are shown in Table III for the normal group and Table IV for the toxemic group.

All of the patients had urine specimens collected at thirty and sixty minutes after injection of the hippurate. On 28 of the normal and 13 of the toxemic patients, the output during the second hour after injection was also determined. The tabulated figures indicate what percentage of 2.0 gm. of hippuric acid was excreted in any one period, and for every case the total percentage in the first hour is given. This last figure is the only one given in Tables I and II.

On scanning the figures in Table III for the percentage excretion of hippuric acid at 30, 60, and 120 minutes after intravenous sodium hippurate given to normal pregnant women, it is apparent that elimination is rapid. The averages are 58.2 per cent for the first period, 20.7 per cent for the remainder of the first hour, and but 10.3 per cent in the 28 instances where the second hour output was analyzed. If it were possible to be sure of a total urine collection for the first half-hour, it is fair to assume that this would be the most significant period. When, however, the urine volume is small, a residual of a few cubic centimeters carries over a high

TABLE IV. TOXEMIC SERIES

CASE	AGE	GRAVIDA	GESTATION*	PER CENT EXCRETION HIPPURIC ACID AFTER INTRAVENOUS SODIUM HIPPURATE				CLASSIFICATION
				30 MIN.	30-60 MIN.	60-120 MIN.	TOTAL FIRST HR.	
1. H. B.	24	i	-117	74.0	5.0	4.5	79.0	L. M.†
2. A. W.	34	ii	- 58	50.0	20.5	13.5	70.5	
			- 30	44.5	17.5		62.0	L. M.
3. L. M.	29	i	- 1	49.0	13.5		62.5	E. S.
4. A. B.	20	ii	- 2	11.0	6.5		17.5	L. M.
5. R. D.	32	iv	- 97	28.5	22.5		51.0	E. S.
6. H. B.	20	i	-152	54.0	22.5	9.5	76.5	L. M.
7. L. B.	35	i	- 50	67.0	10.5	8.5	77.5	L. M.
8. D. H.	28	iv	- 66	66.0	15.5		81.5	E. S.
9. H. Dis.	24	i	- 56	69.0	16.0	8.0	85.0	E. M.
10. E. M.	26	i	- 72	61.0	16.0	11.5	77.0	L. M.
11. P. B.	27	iii	- 64	30.0	39.0	15.5	69.0	E. M.
12. V. S.	23	ii	-120	82.5	17.0	8.0	99.5	E. M.
13. S. E.	19	i	- 7	57.5	15.5		73.0	L. M.
14. L. D.	17	i	- 39	33.5	33.5	14.0	67.0	E. M.
15. E. C.	21	i	-104	67.0	15.5	8.0	82.5	E. M.
16. M. S.	25	i	- 34	48.5	21.5		70.0	E. M.
17. O. S.‡ 18	29	ii	- 2	38.0	15.0	8.0	53.0	L. M.
18. O. S. 20	34	viii	- 6	30.0	33.0	12.0	63.0	E. M.
19. O. S. 24	42	v	- 34	11.0	20.0		31.0	L. M.
20. O. S. 23	22	i	- 1	6.0	23.0		29.0	E. M.
			+ 10	26.0	36.0		62.0	
21. E. B.	16	i	- 35	47.0	19.0		66.0	E. M.
			+ 57	73.0	16.0		89.0	
22. M. C.	20	i	- 13	11.5	38.5		50.0	L. S.
			+ 22	48.5	20.0		68.5	
23. J. R.	27	i	- 14	28.0	28.0	26.0	56.0	L. M.
			+ 10	58.5	25.5	7.5	84.0	

*—, Days before delivery; +, days after delivery.

†E, early; L, late; M, mild; S, severe.

‡O. S., from earlier series.[1]

concentration of hippuric acid to the next half-hour. It therefore seems necessary to take the total output of the first hour for the basis of comparison. No relationship was observed between the volume of the urine specimens and their hippuric acid content.

The average first hour excretion for the 14 post-partum observations is 75.1 per cent, and the average ante-partum value for these same patients is 75.9 per cent. Two patients showed increases from low ante- to high post-partum levels, 1 an increase at a high level, 8 no change, and 3 moderate decreases at the higher level.

It would have been of interest, and the data herein presented might have been more significant through comparison, if a series of intravenous sodium hippurate tests could have been made on normal and nephropathic nonpregnant individuals, but such material was not available during the course of this study. While the standard normal excretion rate remains conjectural, the results here given suggest a tentative index of renal function by this test.

On the basis of the present material, a 60 per cent output of hippuric acid in the first hour seems acceptable, subject to further proof, as the lower limit of normal excretion. But 2 of the 58 ante-partum observations on normal patients fall below this level and these rose above it post partum. Two of the post-partum tests yielded values close to but above, the rest well above, 60 per cent.

The toxemic patients (Table IV) show a somewhat lower average first hour ante-partum output, 64.5 per cent, and 6 patients, a considerably higher percentage than in the normal group, fall below the 60 per cent level. Half of the latter had post-partum tests and showed returns to above the 60 per cent level. The small number of cases and the borderline character of the toxemia at the time of most of the tests forbids any assumptions from these figures.

When the first-hour excretion of hippuric acid after intravenous hippurate in the normal patients is plotted against their weights or surface areas a distinct tendency toward an inverse relationship is shown. This would suggest that the rate of excretion of hippuric acid is proportional to its concentration in the body, and that for highly accurate determinations the dose of sodium hippurate should be graduated according to body size. The range of values obtained with the 2 gm. equivalent dose is not great enough, however, to invalidate the present figures.

III. *Excretion of Uric Acid and Blood Chemistry Observations During the Conjugation and Excretion of Benzoic Acid.*—Urine uric acid outputs in milligrams per hour and blood chemistry determinations in mg. per 100 c.c. in Tables I and II, are omitted for lack of space.

The hourly excretion of uric acid before and after giving sodium benzoate was determined ante partum 38 and post partum 6 times on normal patients, and ante partum 8 times and post partum 1 time on the toxemic group.

The urine uric acid shows a rapid fall to a minimum in the second or third hour after sodium benzoate. By the fourth hour excretion has usually begun to rise again. The average uric acid excretion curve for the normal ante-partum group is shown in Chart 1. The few observations post partum and on toxemic patients follow this curve closely. When the normal ante-partum group is divided into those with hippuric acid outputs of more than 2.69 gm. and those with less than 2.70 gm. the uric acid excretion of the former division shows a quicker, of the latter a slower, recovery at the fourth hour.

The effect of sodium benzoate on the twenty-four-hour excretion of uric acid was demonstrated in a forty-eight-hour observation period on one patient (A. F., No. 27, Table I). Chart 2 shows how in the middle of the period during the formation and excretion of hippuric acid the uric acid output is depressed only to become accelerated thereafter, bringing the second twenty-four hours' total to approximately the same level as for the preceding control period.

These results do not differ from those expected in nonpregnant individuals. In any given case the drop in uric acid excretion may be taken as a secondary index of the aborption of the benzoate.

Blood uric acid determinations were made on 26 occasions ante partum and 6 times post partum before and two hours after giving sodium benzoate to normal patients and on 5 and 1 occasions, respectively, in the toxemic group. Analysis of

the normal ante-partum group shows an increase from an average of 2.61 mg. per cent before to 2.82 mg. per cent after the benzoate. In 4 instances there was a decrease, in 1 no change, in the rest increases.

Blood urea nitrogen and/or nonprotein nitrogen was determined simultaneously with the blood uric acids ante partum 20 times. There were some scattered observations post partum and on toxemic patients. These values show a tendency to change

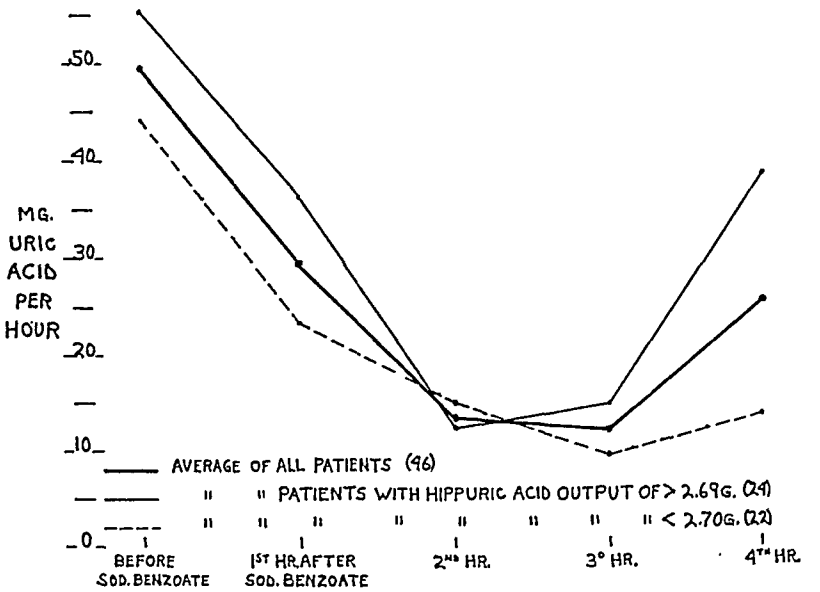


Chart 1.—Excretion of uric acid after sodium benzoate by mouth.

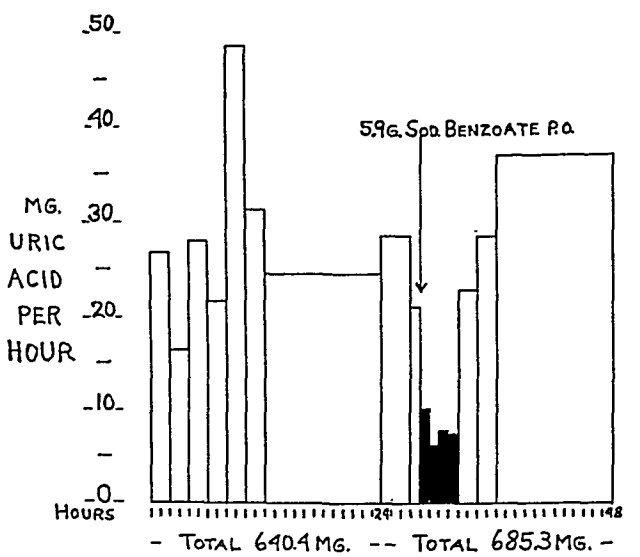


Chart 2.—Forty-eight-hour excretion of uric acid.

in a direction opposite to the uric acid. Seventeen urea nitrogen analyses showed a decrease in the average from 7.27 mg. per cent before to 6.77 mg. per cent at the second hour. Eight decreased, 6 did not change, 3 increased. The average of 16 nonprotein nitrogen values was 23.03 mg. per cent before and 20.95 mg. per cent at the second hour. One showed no change, all the rest decreased.

The significance of the changes in the blood urea and nonprotein nitrogen is not apparent without knowledge of concomitant excretion rates of urea and other nitrogen fractions.

A few blood chemistry analyses four hours after sodium benzoate indicated that the above changes would generally be found more marked at that time.

CONCLUSIONS

It is apparent that a large number of pregnant women exhibit significant deficiency in the excretion of hippuric acid after sodium benzoate is given by mouth.

That this is not usually due to the failure of this substance to pass through the kidneys is predicated by the generally normal excretion of hippuric acid when it is introduced by vein.

The most instructive data of this study are derived from those patients who had both tests ante and postpartum. (Cases No. 59 to 70, Table I; 20 and 21, Table II.) Of the normal group, cases 64 and 67 yielded low antepartum values for both tests, while both tests in both patients returned to normal post partum. One of the toxemic patients (Case 21, Table II) showed low values for both tests ante partum just before the development of severe preeclamptic symptoms. Her intravenous hippurate test was normal post partum, but the excretion after sodium benzoate, while increased, remained subnormal. Although all other patients in these two series had normal ante- and post-partum excretion of the intravenous hippurate, 5 showed subnormal ante-partum excretion after sodium benzoate, returning to normal post partum, and most of those at the normal level ante partum excreted considerably more post partum.

Thus, in the synthesis and excretion of hippuric acid in pregnancy it is possible for either or both phases to be disturbed, and although in the majority of normal cases, at least, there is probably no nephric barrier to hippuric acid, in any one instance a deficient recovery of hippuric acid after sodium benzoate by mouth is not acceptable evidence of a disturbed detoxifying mechanism until it is demonstrated that hippuric acid as such can be freely eliminated. If a low output of pre-formed hippuric acid is found by the intravenous test, that fact may have some significance as an index of renal function, but it becomes impossible to interpret the sodium benzoate test.

The incidence of depressed synthesis and excretion of hippuric acid after sodium benzoate was not related to the well-being of the patients in this group, nor to the development of toxemia or other complications of pregnancy.

It was previously suggested[1] that because of other physiologic changes in pregnancy it might not be strictly correct to interpret this test as an index of liver function. Some other liver function tests seem to give a similar incidence of low values in pregnancy,[16] while still others show no or indeterminate changes.[17] Certainly the application of this test to hepatic disease complicated by pregnancy could be expected to yield considerable confusion, though, even then, repeated tests (with corollary demonstration of adequate elimination of hippuric acid) could have some value in showing progress.

SUMMARY

1. The excretion of hippuric acid after sodium benzoate by mouth was found to be subnormal in more than half of a group of women with un-

complicated pregnancies. A smaller group of patients who developed toxemia showed a somewhat higher incidence of the same depressed function.

2. Post partum the same test shows increased yields of hippuric acid in almost all cases, and, similarly, a return to normal by those giving low ante-partum values.

3. With few exceptions hippuric acid was excreted rapidly when given intravenously as the sodium salt to normal pregnant women. Forty per cent of a small group of toxemic patients showed diminished excretion by this test.

4. The intravenous hippurate test showed no significant changes post partum as compared to the ante-partum results, except in cases having low ante-partum yields when the tendency was to return to normal.

5. The possibility of depressed kidney response to hippuric acid in pregnancy makes it necessary to check renal function in order to interpret the result when a subnormal value for hippuric acid excretion is obtained after sodium benzoate by mouth.

6. Analysis of the urine for hippuric acid after giving sodium hippurate intravenously is recommended as such a check.

7. The ingestion of sodium benzoate in pregnancy is followed by changes in the blood and urine uric acid levels similar to the changes so produced in nonpregnant individuals.

I wish to acknowledge gratefully the cooperation of J. W. Mull, Ph.D., at Maternity Hospital, and of Miss Helen R. Fowler, R.N., at the Florence Crittenton Home.
The Mallinckrodt Chemical Works, St. Louis, Mo., kindly provided the sterile sodium hippurate solution used in this study.

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MORBIDITY FOLLOWING RADICAL OPERATIONS FOR PELVIC INFLAMMATORY DISEASE*

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IT HAS always been the policy of the gynecologists at the Mayo Clinic to treat acute pelvic inflammatory disease, when there was no question about the diagnosis, conservatively, employing the medical regimen in vogue at the time. As time went on and as methods of diagnosis and treatment improved, fewer and fewer patients needed surgical treatment. This was especially true of patients with the gonorrheal type of pelvic disease. Since we have had the chocolate blood-agar culture medium to depend on, it has been possible to put many more patients into this definite group. Sulfanilamide, and when that alone fails, added fever treatment, will care for the great majority of early gonorrheal infections before large pelvic masses have developed. If pelvic masses are already present, vaginal Elliott treatment or diathermy will reduce the number of cases requiring surgical treatment. In fact, so much more can be done in a medical way at present for pelvic inflammatory disease that this paper may not seem timely. There are, however, certain types of conditions that will always be surgical problems: those in which the appendix cannot be ruled out, those in which unilateral adnexal disease follows appendicitis or streptococcal infections, and, lastly, those in which patients continue to have symptoms and pelvic masses after a regimen of active medical treatment has been carried out.

One purpose of this investigation was to try to help us decide in this last-named group of cases whether conservative or radical surgical treatment was to be favored. We have been aware that, following conservative surgical procedures, many patients in this group have continued to complain of symptoms similar to those they had prior to operation. Some for a time have had more menstrual irregularity than before operation. We wanted to know whether these symptoms were possibly due to a temporarily disturbed ovarian function due to postoperative inflammation, and what the final outcome was. Of incidental interest was the problem of seeing if we could add anything to our knowledge of the symptoms associated with decreased or failing ovarian function.

We therefore chose a group of cases in which the patients were operated on between Jan. 1, 1925, and Jan. 1, 1935. We felt this would take all of them beyond the so-called latent period following operation which we had noticed lasted in some cases about two years. Every patient in this series, therefore, had been operated upon at least three

*Submitted for publication, August 4, 1938.

years prior to the time of our follow-up study. The indications for surgical treatment had been inability to control the symptoms or to reduce pelvic masses, or both, by medical means. A few patients had been operated upon early because the appendix could not be ruled out as the primary cause of the condition. The chief presenting symptoms had been the usual ones: pelvic pain (worse with menstruation) and menstrual disturbances, chiefly menorrhagia, and vaginal discharge. A few patients had been concerned chiefly about sterility. In every case there was a fairly good history of pelvic inflammatory disease, the condition having been initiated by a more or less severe attack of pain, with fever, vaginal discharge, and urinary symptoms; the positive pelvic findings were adnexal masses or a tender uterus partially fixed in retroversion with tender palpable adnexa.

Three hundred patients were operated upon during this ten-year period (Table I). We divided this series in several ways, considering etiology, age, and the type of operation (Tables II, III, IV). We have fairly reliable follow-up data on 183 of these patients, which data were obtained on re-examination of the patients, from correspondence, or from a recent questionnaire that was sent out. We are aware of the limitations of this questionnaire method, yet when a patient answers that she has been perfectly well since operation, as many of them in our series did, one would certainly accept the result as satisfactory.

TABLE I. SUMMARY OF MISCELLANEOUS DATA

	PATIENTS
Total operated upon	300
Came to operation with draining fistulas or sinus tracts	15
Died in hospital after operation	7
Developed postoperatively intestinal obstruction	2
Died from obstruction following operation	1
Developed sinus tracts following operation at clinic	3
Developed chronic phlebitis following operation	2
Developed an acute exacerbation following operation	6

TABLE II. TYPE OF SURGICAL TREATMENT WITH REFERENCE TO PATIENT'S AGE AND TYPE OF INFECTION

TYPE OF INFECTION	CONSERVATIVE AGE, YEARS		RADICAL AGE, YEARS	
	-30	+30	-30	+30
Appendiceal	7	4	1	
Postabortal	12	8	2	1
Gonorrheal	4	6	5	5
Indeterminate:				
1. Within 2 weeks after onset*	10	9		3
2. Two weeks to 6 months after onset	7	15	3	7
3. Six months to 1 year after onset	11	11		2
Old infection	24	17	2	7
Total	75	70	13	25

*Of pelvic inflammatory disease.

Though we have presented in Tables III and IV only the final complaints of the patients after at least a three-year period, we have records of the complaints of many of them for the first two years after the operation. These data bear out our surmise that for a certain period following a conservative pelvic operation for pelvic inflammatory disease, the patient often continues to have pelvic symptoms characterized by menstrual irregularities, and particularly, menorrhagia. This latter is the most usual symptom complained of; it occurred in more than 10 per cent of our cases and was no doubt due to the inability of the disturbed ovaries to function normally. Other patients complained of pelvic pain and backache, worse with the menses, and of a discharge. When a woman continues to have any of these troubles following a pelvic operation, she becomes very discouraged. If only the discharge continues, it of itself is annoying enough to make her feel she has not been cured. It may be only a vaginitis due to Trichomonas or Monilia, and while the surgeon could not cure it, he nevertheless gets the blame for not having done so.

TABLE III. MORBIDITY FOLLOWING CONSERVATIVE OPERATIONS FOR PELVIC INFLAMMATORY DISEASE

OPERATION	PATIENTS	POSTOPERATIVE COMPLAINTS			SUBSEQUENT TREATMENT NECESSARY		PREGNANCIES
		IRREGULAR MENSES	DISCHARGE	PELVIC PAIN	SURGICAL	MEDICAL	
Plastic operation. No organs removed	10	1	1	3		1	
Removal of one tube	9	2	5	6			2
Removal of adnexa on one side	49	11	13	19	7	3	14†
Removal of both tubes	21	9	7	12	1	4	
Removal of tubes and one ovary	43	15	13	21	3	3	
Removal of both tubes and ovaries	13	4	3	4	2	4	
Total	145	42	42	65	13*	15	16

*Minor operations only (dilatation and curettage) in 3 cases; in remainder, surgical procedures.

†Ectopic in 1 case.

TABLE IV. MORBIDITY FOLLOWING RADICAL OPERATIONS FOR PELVIC INFLAMMATORY DISEASE

OPERATION	PATIENTS	POSTOPERATIVE COMPLAINTS			SUBSEQUENT TREATMENT NECESSARY	
		IRREGULAR MENSES	DISCHARGE	PELVIC PAIN	SURGICAL	MEDICAL
Removal of organs except one ovary	20	0	4	4	0	1
Removal of all organs,* panhysterectomy	18	0	4	3	0	2
Total	38	0	8	7	0	3

*Subtotal hysterectomy in 2 cases.

In cases in which one ovary or a part of one ovary and the uterus was preserved, the patients apparently have had the most stormy postoperative course; it usually takes several months to get them righted, if indeed they ever do. They will often present, for a time at least, all of the symptoms associated with failure of ovarian function: menstrual irregularities, oftener of the menorrhagic but occasionally of the amenorrheic type; soreness of the breasts before periods, dysmenorrhea, premenstrual nervousness and depression; headache with the periods, and vasomotor disturbances following the periods. One of the most distressing of these postoperative complications is menorrhagia. In our group of cases 33.3 per cent of the patients complained of irregular bleeding postoperatively. Would it not be well to avoid this complication by removing the uterus too, since it is of no more functional value after bilateral salpingectomy? Our figures show that hot flushes were increased only 10 per cent in those women whose uterus was also removed. After a time the ovary, if there is sufficient good tissue left in it, will begin to function more normally and these disturbances do tend to disappear.

Considerable can be done in a medical way to tide these patients over this so-called latent period. The menorrhagia can often be controlled with luteal hormone and calcium, and the ovarian circulation can be improved by vaginal heat, which likewise helps the pelvic pain, soreness and backache, and at times the residual discharge. If the cervix has not been cauterized at the time of operation, cauterization, carried out in the office, may later be necessary. We believe that when conservative surgical treatment is being contemplated, or after it has been carried out, it is wiser to tell the patient that it may be some time before her periods become regular and that she may need further medical treatment.

Another interesting supposition has been supported by our follow-up study: Women who have pelvic inflammatory disease, and who have had (and sometimes have not had) surgical treatment, are very likely to reach the menopause earlier than other women. Six of our 10 patients who had only plastic operations reached the menopause before forty-two years of age. By a "plastic operation" we mean that neither ovary was entirely removed though in a few cases resection was employed. One patient ceased menstruating at the age of twenty-seven and one menstruated only once after her operation at the age of twenty-eight.

This last woman's case was interesting. She had had her appendix and part of an ovary removed seven years prior to her pelvic operation at the clinic. Three years later she had had a spontaneous miscarriage, after which she had an attack of lower abdominal pain with fever and discharge. She continued to have more or less constant lower abdominal discomfort, worse with the menses, and a profuse menstrual flow lasting from eight to ten days. When the surgeon explored the pelvis he performed only an internal shortening operation. A note was made at the time that there was evidence of chronic pelvic inflammation but the fimbriated ends of the tubes were open, so they were left undisturbed. This was in July, 1926. In October the patient wrote that the operation "had done no good." She was having pain and

had menstruated only once. In May, 1929, she wrote again that she was still having discomfort. In the recent questionnaire we sent her, however, she said she had never had any periods since the operation nor had she had any hot flushes; in other words, ten years after the operation she had no complaints at all.

There were 132 cases in which enough ovarian tissue and uterus were left so that the menses could continue. Twenty-six of the patients, however, had ceased menstruating and were having hot flushes before the age of forty years. One of these patients, who had been operated upon for unilateral adnexal disease, had a normal pregnancy, labor, and parturition at the age of thirty-four years. Her periods were irregular after this. She is now forty-one years old and has had a few hot flushes in the past two years. The number of those whose menses ceased early is higher than the number of those who had flushes; in fact, not one woman in this group who had ceased menstruating complained much of flushes. In contrast to those who ceased menstruating, we would like to mention one patient in this group who was operated upon in 1926 at the age of thirty-two years.

She had been ill for eight months before operation. The surgeon removed both tubes and ovaries, transplanting what he felt was still good of the right ovary into the right rectus muscle. The patient returned to the clinic in March, 1928, two years later, because she had found a small lump in her breast. At this time she said her menses had been regular, lasting two days, but that for the seven months previously she had been having some irregular bleeding between periods. There was a firm nodular uterus (so described by the examining doctor) and in the right rectus muscle was palpable a small mass measuring 2 by 3 cm. No mention was made regarding any tenderness or swelling of the mass with the menses. Nothing was done about the irregular bleeding, it being considered to be due to small fibroids. The small tumor in the right breast, which was benign, was removed. When last heard from (in May, 1938), nearly twelve years after her operation, this patient said that her periods were regular and that she had had no hot flushes and had no other complaints. One would hardly expect the transplanted ovary to carry on so well but this occasionally must happen.

Naturally in this whole group were women with extremely acute pelvic inflammatory disease who were operated upon early when it was not possible to dissect out structures.

One woman, only twenty-two years of age, was operated upon in 1931. She had had trouble for four months. She mentioned in the questionnaire having had a few hot flushes. Another patient, twenty-three years old, who had had trouble for five years (gonorrhea) was operated upon in 1930 for bilateral tubo-ovarian abscesses; these were drained twice before the radical operation was carried out. This patient said in the questionnaire that she had had no flushes or other complaints and was married. It is possible, of course, that she may have a piece of ovary left.

Comparing the group of cases in which one ovary and the uterus was left with the so-called radical group in which everything was removed except one ovary, 21 per cent of the patients who underwent conservative surgical treatment and in whom the uterus was left had hot flushes early and 31 per cent with only an ovary left had an early menopause. None of these patients complained much of the hot flushes.

The small group of 13 patients in whom the tubes and ovaries were removed, but in whom the uterus was left, was very interesting. In all these cases the disease was extensive and large tubo-ovarian abscesses were present. That was the reason for leaving the uterus. Three of these women stated in the recent questionnaire that they were still having regular periods and no hot flushes. Another patient had regular periods for seven years (1927 to 1934) after her operation, and has had no flushes; the surgeon made a note that he thought that he had removed both ovaries but that there was so much infection he could not be sure of this. Four women had irregular bleeding after the operation; 2 of these had to undergo hysterectomy (elsewhere), and 2 had to be given radium (also elsewhere). Of the whole group of women, those who complained most of flushes were the remaining women in this group who had both ovaries removed and those of a second group who underwent panhysterectomy. This would be expected, yet 6 women out of 18 who underwent panhysterectomy apparently had no hot flushes after operation, though 31 per cent of these patients were operated upon before they were thirty years of age. Strange as it may seem, only 1 patient complained bitterly of flushes, saying that they had occurred every forty-five minutes for nine and a half years; this patient was thirty-seven years of age when operated upon.

Our results have substantiated the fact that when both tubes are involved in the inflammatory process it is unusual for pregnancy to occur. In all of our cases in which pregnancy occurred, one adnexa only was involved. In 10 of these cases the etiologic factor was definitely either appendiceal or the infection developed post partum, 2 patients had apparent gonorrheal infection though this was not proved, and in 1 case it was impossible to tell what the cause of the condition was. It is interesting that of all the patients with proved gonorrhea, every one was found by the surgeon to have both tubes involved. Both tubes were removed in every case except one, that of a woman operated upon in 1931 at the age of thirty-one years who had suffered from the disease for nine and a half years. Because the left tube appeared to be in fair condition, it was left undisturbed. This woman recently reported that she had not become pregnant and still had a pain in her left side similar to that which she had had in her right side before her operation.

In our final results of morbidity we considered only those complaints that seemed directly referable to the pelvic organs, such as menstrual irregularities, too frequent or too profuse periods, pelvic pain similar to that before operation or pain made worse by menstruation, continuance of a troublesome discharge, exacerbations of the infection (which occurred in six instances), or whether further active medical treatment or operation had been necessary. We have not considered the vasomotor disturbances or any subjective symptoms.

COMMENT

We would like to make a few comments only in summary as we have not followed a sufficiently large series of patients as yet to feel justified in drawing positive conclusions. Our statistics seem to reveal:

1. So-called plastic operations on the pelvic organs after pelvic inflammatory disease are useless, especially plastic operations on the tubes. Pregnancies do not follow and the patient is often not relieved of her symptoms.

2. There is a definite morbidity after conservative operations for pelvic inflammatory disease but, in the future, with all the means at our command, this should be less than it has been in the past. Good medical treatment before and following such conservative surgical treatment should lessen this morbidity.

3. When there has been extensive pelvic inflammatory disease, with apparent involvement of the ovaries as well as the tubes so that little good ovarian tissue is left, it would seem best to remove the uterus, leaving the patient what ovarian tissue can be left. This saves her from having irregular, often profuse and painful periods. We feel that it is better to save the uterus if there appears to be reason to believe that one ovary will function normally, but it would appear as if several of the women in this series with only one ovary and the uterus left would have been better off with the uterus out. One young woman in our series was so operated upon at twenty-eight years of age (in 1926) after ten months of invalidism following a septic abortion and with all the active treatment we knew at the time to give. She married at the age of thirty-two and says her sexual life is normal. She also says that she has never had any hot flushes.

4. Unilateral pelvic inflammatory disease is usually the result of appendiceal or post-partum infection and, when such is the case, the removal of the affected adnexa improves the patient's general and pelvic conditions and her chances of becoming pregnant.

Mekler, A.: Experiences with the Hormonal Pregnancy Reactions of Aschheim-Zondek and Friedman-Lapham, Monatschr. f. Geburtsh. u. Gynäk. 107: 257, 1938.

In the Zürich University Woman's Clinic 1,360 hormone pregnancy tests were performed from 1930 to 1935. Of this number 676 tests were performed on mice and 684 on rabbits. The mouse test was correct in 96.6 per cent of the cases and the rabbit method in 93.1 per cent. If the doubtful reactions are eliminated the respective percentages are 97.8 for the mouse and 97.4 for the rabbit tests. Both tests are positive in a large proportion of pregnancies within eight days after a missed period. In cases of abortion and ectopic pregnancy the positive reaction disappears proportionately to the severity of the symptoms. If an abortion is rapidly completed or an ectopic pregnancy quickly removed, the tests become negative very quickly. The author believes that both tests should be employed. In most cases of pregnancy the mouse test should be used but where it is important to obtain a rapid result the rabbit test is preferable.

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THE MANCHESTER (PARAMETRIAL FIXATION) OPERATION FOR CURE OF PROLAPSE AND CYSTOCELE*

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IN 1888, Donald of Manchester, England, began to treat uterine prolapse by combining anterior and posterior colporrhaphy with amputation of the cervix. Previous to this, the operative procedures utilized in curing prolapse consisted either of some sort of vaginal shortening or of cervical amputation, but very seldom a combination of the two. As a matter of fact it is interesting to note that before the turn of the last century, the majority of cases of prolapse were not treated surgically at all. Pessary insertion was the method commonly employed, and perineorrhaphy was done on occasion to enable the patient to wear a ring pessary. At present, the indication for the use of the pessary should be limited to patients, young or old, who suffer from medical diseases contraindicating surgery.

The variety of operative procedures used in curing uterine prolapse is testimony to the fact that for many years no one method applicable to the great majority of cases has been developed. The choice of operation has usually been determined by the age, parity, and social status of the patient. Vaginal, abdominal, or a combination of the two methods of surgical approach have been utilized with varying degrees of success.

The operations devised for the cure of prolapse which are most commonly employed today include vaginal hysterectomy, Watkins interposition operation, abdominal fixation of the uterus, LeFort's colpocleisis, and colporrhaphy. The objections to the fixation operations are obvious to all gynecologists who have had experience with these methods. In a series of 200 ventrofixations cited by Frank, 21, or 10.5 per cent, developed postoperative ventral hernia. Vaginal hysterectomy carries with it a mortality of 1 to 2 per cent. Aside from this, extirpation of the uterus removes the best anatomic support for the bladder. It is not unusual in our clinic to find recurrent cystoceles in spite of high, well-supported vaginal vaults following vaginal hysterectomy; and post-operative prolapse of the vaginal vault taxes the resourcefulness of the best gynecologist. Further, removal of the uterus in premenopausal years causes a cessation of menstruation, with its attendant psychic disturbances; and hastens the climacteric. Kretzschmar and Gardiner have shown that hysterectomy with ovarian conservation in women thirty-six years of age or less was followed by menopausal symptoms before 40 years of age in approximately 60 per cent of the patients. Vaginal hysterectomy for the treatment of prolapse is best adapted when there is associated uterine pathology. The Watkins interposition operation

*Presented before the Chicago Gynecological Society, May 20, 1938.

has given good results in the treatment of prolapse, but the procedure involves invasion of the peritoneal cavity and may require sterilization. It is also important that the uterus be neither too small nor too large in order to fit properly into the pubic arch, and amputation of the cervix is usually necessary for a good result in a large percentage of the patients. The LeFort colpocleisis operation has obvious limitations, but where indicated, gives gratifying results. Anterior and posterior colporrhaphy alone tighten the weakened pelvic fasciae, but the presence of an elongated cervix acts as the long arm of a lever which brings the long axis of the uterus into a line with the vaginal axis and thus predisposes to recurrent prolapse.

In 1928, Baer and Reis analyzed 220 operations for prolapse performed by members of the gynecologic staff of the Michael Reese Hospital. The operation most often employed in this series was the Watkins interposition operation, performed in 91 patients, with complete success in 87.5 per cent of the cases. There was one death and the gross morbidity was 55.1 per cent. In 1937, Baer, Reis, and Laemmle analyzed a subsequent comparable series of prolapse cases and found that the trend in the treatment of uterine prolapse at the Michael Reese Hospital in ten years had shifted from the interposition operation to vaginal hysterectomy. The results of this operation showed success in only 70.7 per cent. There were 2 deaths and a gross morbidity of 50 per cent. As the authors point out, the operation to which the staff turned to improve its results in the cure of prolapse, namely, vaginal hysterectomy, was attended by a much smaller percentage of cures (70.7 per cent) than the operation used most often previously, namely the Watkins interposition operation (87.5 per cent).

In recent years, the staff at the Michael Reese Hospital has utilized the Manchester operation as the procedure offering the best results in the greatest number of cases. The attention of the medical profession in this country was first directed to this operation by Frank, who in 1932 published a preliminary report. In this article, the author reviewed a large series of cases of prolapse treated by a variety of other operations. The results in this group were satisfactory in 66 per cent of the patients and good in only 46 per cent; and because of this the need for a better operative treatment was stressed. Mestitz in 1932 also described an operation similar in principle to the Manchester and used by Halban in his clinic since 1919. The Manchester operation has been employed for the treatment of prolapse in the British Isles for over forty-five years, having been introduced by Donald, and reported on at various times by Fothergill and Shaw.

Between Dec. 15, 1935, and Jan. 1, 1938, there were 51 Manchester operations performed at the Michael Reese Hospital by seven operators. The operations so classified were those in which the typical parametrial fixation stitch was used. In our analysis of case records we found many patients scheduled for Manchester plastics preoperatively, but since the actual surgical procedure did not include parametrial shortening, we did not include them in our series. The parametrial fixation was most commonly performed in association with cervical amputation but in a few cases the cervix was left in situ.

The chief primary indication for the performance of the Manchester operation is prolapse of the uterus. It is often difficult to agree on the

exact extent of uterine prolapse in any given patient, since variations in the size and length of the cervix influence the opinion of the examiner. It is not uncommon to find divergent opinions as to the degree of prolapse expressed by various examiners, when the patient is examined more than once. Fear, nervous tension, etc., may cause marked contraction of the voluntary muscles in the pelvic and urogenital diaphragms and thus prevent the uterus from descending with strain. On the other hand, if the patient is completely relaxed at a subsequent examination, the cervix may descend far beyond its former position. We have repeatedly witnessed the appearance of the cervix beyond the vestibule under general anesthesia where previously the most severe straining by the patient did not deliver it out of the vagina. On our service, we classify as first-degree prolapse, descent of the normally-sized cervix to the level of the ischial spines; second-degree prolapse, descent to the vestibule; third-degree prolapse, descent outside the vagina; and procidentia or complete prolapse, descent of the corpus uteri outside the vagina. It is obvious that a uterine corpus may be normally placed, but its elongated or hypertrophied cervix may protrude from the vulva. The over-sized cervix is tissue below the insertion of Mackenrodt's ligaments into the uterus and since the parametrium is intact, the uterine prolapse is in reality only apparent. Clinically, however, the symptomatology and treatment is similar to cases of true prolapse. The performance of parametrial fixation with cervical amputation in cases of elongated and hypertrophied cervix is valuable, in that it sharply anteflexes the remaining corpus, thus preventing descensus.

In our series of 51 patients, the primary indication for performing the Manchester operation was uterine prolapse in approximately four-fifths of the cases (41 or 80.4 per cent). Elongation of the cervix was a very frequent accompaniment of the prolapse. Hypertrophied, elongated, and lacerated cervix was the primary operative indication in 4, or 7.8 per cent, of the cases, and cystocele was the primary operative indication in 6, or 11.8 per cent. Cystocele, in itself, is probably the most common form of pelvic prolapse. Its production during labor, implies a break at the so-called "weak-spot" in the uteropubic fascia, and since this fascia is continuous with the fascia incorporated in the bases of the broad ligaments, the bladder hernia may be a forerunner of true uterine prolapse. Prolapse of the bladder, furthermore, increases the

TABLE I. INDICATIONS FOR MANCHESTER (PARAMETRIAL FIXATION) OPERATION

PRIMARY INDICATIONS	NO.	TOTAL %	ASSOCIATED PATHOLOGY				
			CYSTO.	RECTO.	ELONG. CERVIX	HYPERT. CERVIX	LAC. CERVIX
Uterine prolapse	41	80.4					
First-degree	10		10	9	6	1	8
Second-degree	18		18	15	10	1	10
Third-degree	12		12	11	9	1	10
Procidentia	1		1	1		1	
Cervical pathology Elong.; Hypert.; Lac.	4	7.8	1	4			
Cystocele	6	11.8		6	1	1	4
Total	51	100					

vesicouterine space interperitoneally, allowing bowel to be interposed between uterus and bladder. This causes the corpus to fall back into a position of retrodisplacement, which constitutes the first stage in uterine descent. In the patients with cystocele as a primary indication, cervical amputation was done in 4 and the cervix allowed to remain in situ in one. There were 4 other patients in whom the cervix was not removed; 2 with first-degree prolapse and cystocele; 1 with second-degree prolapse and cystocele; and 1 with third-degree prolapse and cystocele. All the cases of prolapse were associated with cystocele.

Parturition is not necessarily an essential predisposing factor of prolapse, which occasionally occurs in nulliparas. Heavy industrial occupations may predispose to descensus in these women by increasing the intra-abdominal pressure or weakening the pelvic floor. Also some patients may manifest a congenital weakness of the fasciomuscular system. Three of the patients in our series with prolapse were nulliparas. One was 51 years of age, and single, who upon straining could deliver the cervix beyond the vestibule. This prolapse was associated with marked pelvic floor relaxation, and a huge cystocele and rectocele. X-ray of the lower spine revealed an occult spina bifida. Another was 23 years of age, married, and manifesting a second-degree prolapse. The third, aged 49, had an elongated cervix with cystocele and rectocele, the cervical pathology being on the basis of an old chronic endocervicitis. The remaining patients were parous, the number of full-term births ranging from 1 to 11 with an average of 3. The youngest patient was 22 years of age, and the oldest 69, the average age being 43. Four patients were under 30 years of age; 14 were between 30 and 40; 20 were between 40 and 50; 11 were between 50 and 60; and 2 were over 60 years of age.

TECHNIQUE OF OPERATION AND RESULTS

The following description is our modification of the original Manchester technique. After the usual preparation as for any vaginal operation, the cervix is grasped with a vulsella and pulled down into the introitus. An inverted "T" shaped incision is made, starting just below the external urinary meatus and circumcising the cervical vaginal mucosa just above the external os. The posterior portion of the circular incision is not completed until the pubocervical fascia has been reconstructed in order to conserve blood loss from the posterior flap. The flaps are dissected laterally exposing the bladder with its overlying weakened uteropubic fascial layer. This is accomplished first by sharp and then by blunt dissection. Marked venous bleeding is usually encountered far laterally and this should be controlled by suture before proceeding. The bladder is next freed from the anterior wall of the cervix and pushed upwards by blunt finger dissection. This maneuver makes prominent the "bladder pillars" of uteropubic fascia on either side (Fig. 1). The angles of the bladder must be carefully dissected upwards in order that the ureters may be completely removed from the danger of ligation (Fig. 3). The bladder hernia is then reduced by uniting the uteropubic fascia with interrupted Lembert's sutures of catgut. Interrupted silk sutures are placed in two planes in the region of the internal vesical sphincter if incontinence is a prominent symptom.

The bladder pillars of each side are caught between two clamps at a level of 1 cm. above the plane of cervical amputation. The top one is placed well laterally and takes in its grasp some cervical and parametrial tissue (Fig. 2). When ligated, this stitch includes fibers of parametrium and uteropubic fascia and marks the location for the parametrial stitches to be placed later on.

The vaginal mucosa is then dissected free from the cervix laterally and posteriorly, and a hemostatic suture is placed on each side, ligating the cervical branches of the

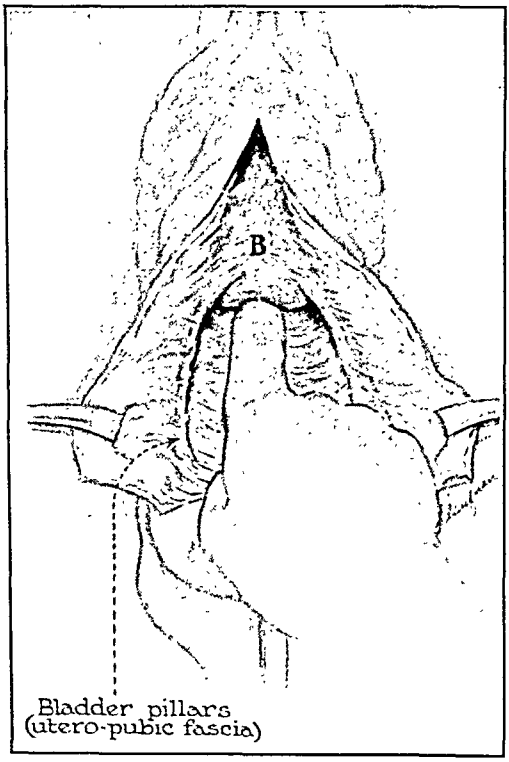


Fig. 1.

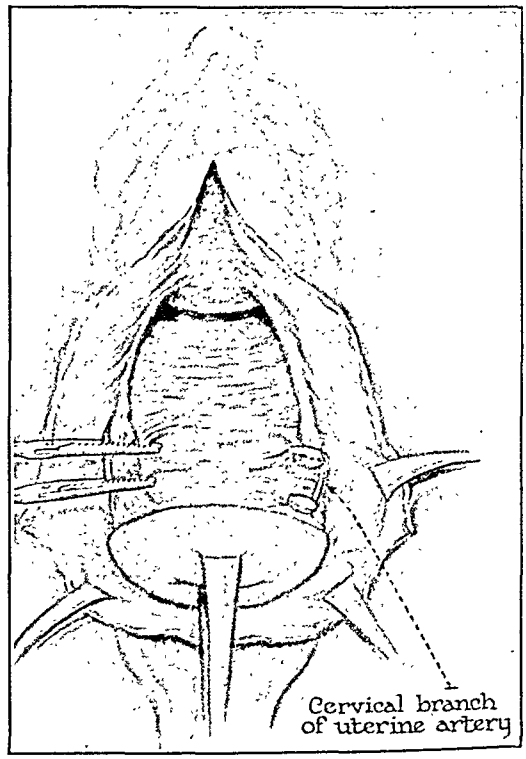


Fig. 2.

Fig. 1.—After an inverted "T"-shaped incision, the bladder is freed from the cervix and dissected upwards, making prominent the lateral portions of uteropubic fascia ("bladder pillars").

Fig. 2.—The "bladder pillars" are clamped, cut, and ligated, the upper clamp including parametrium laterally and some cervical tissue.

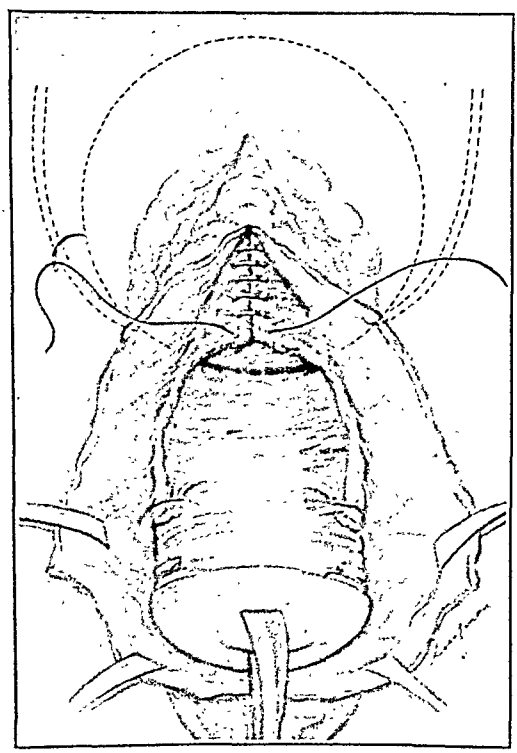


Fig. 3.

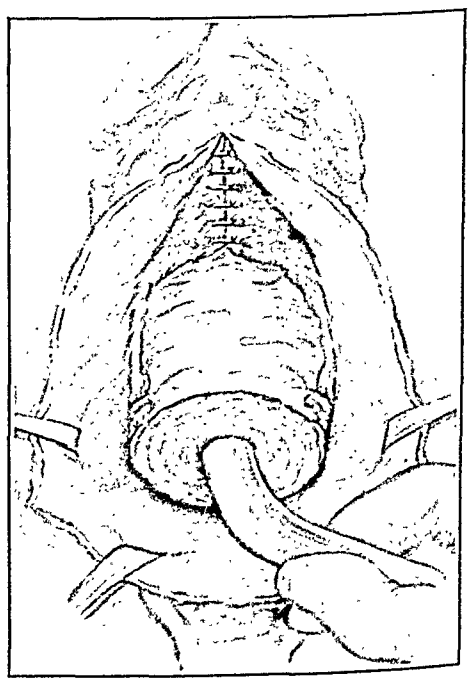


Fig. 4.

Fig. 3.—Illustrating the high position of the ureters away from possible ligature, when the bladder "corners" are carefully dissected upwards.

Fig. 4.—The cervix has been amputated and dilatation and curettage is performed through the clean stump.

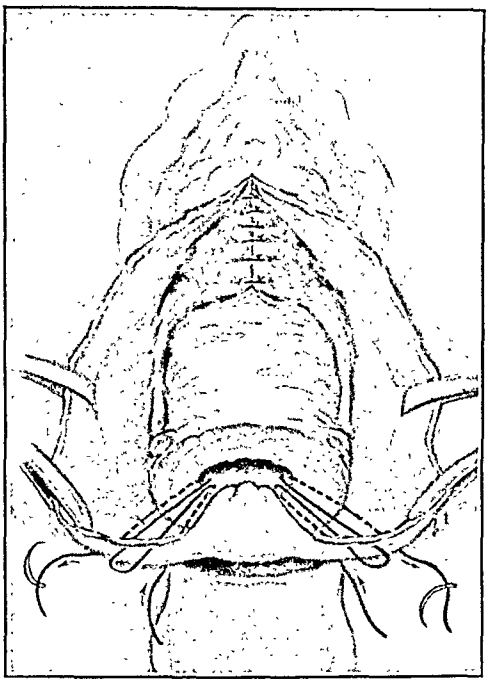


Fig. 5.

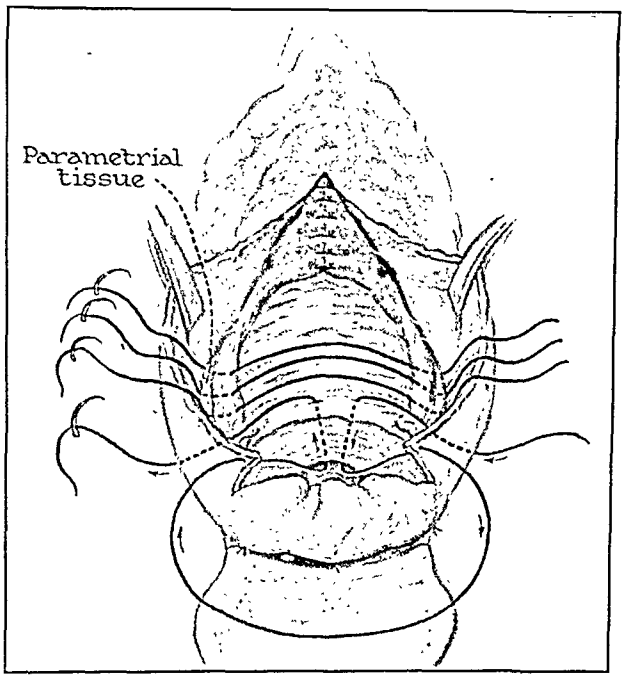


Fig. 6.

Fig. 5.—The posterior and the medioposterior inversion stitches are placed as indicated. This facilitates the placing of the parametrial stitches.

Fig. 6.—The anterior inversion stitch is placed, but not tied until the parametrial stitches are inserted. The parametrial stitches are placed to include the tissue just lateral to the fixed fibers of the uteropubic fascia.

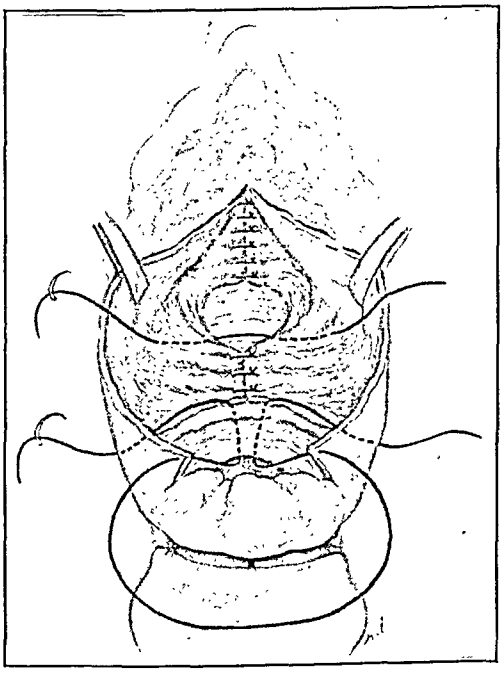


Fig. 7.

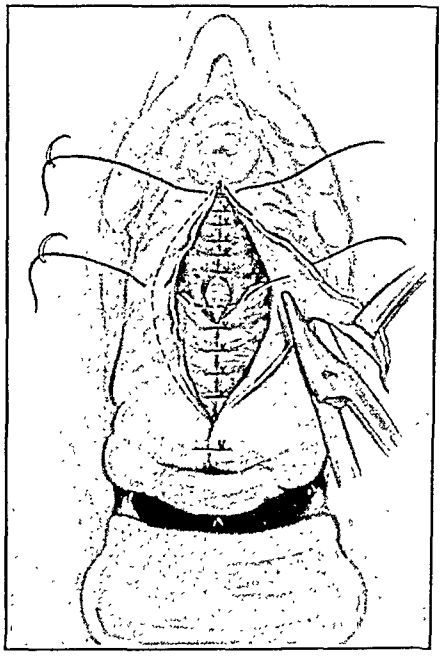


Fig. 8.

Fig. 7.—The parametrial stitches are tied in front of the cervix forcing it backwards. The remaining uteropubic fascia is united in the midline and includes uterine tissue.

Fig. 8.—The vaginal mucosa is trimmed elliptically as indicated. A few interrupted sutures angulate the vaginal mucosa on the uterus, thus further supporting the bladder.

uterine arteries at a level just above the plane of amputation. If a low cul-de-sac is opened into, the peritoneal cavity is closed by a purse-string suture high on the posterior surface of the uterus. The cervix is then amputated circularly or by conical excision. After this, the remaining cervical canal is dilated to a number 12 or 16 Hegar and the endometrial cavity briskly curetted (Fig. 4). Dilatation and curettage after cervical amputation rather than before is not only a simpler and a safer procedure but removal of the infected lower cervix also obviates the forcing of the infectious secretions into the uterine cavity. Wide dilatation also facilitates a more proper inversion of the vaginal mucosa into the cervical canal.

The vaginal mucosa is then inverted into the canal by modified Sturmdorf stitches placed posteriorly and posteriomedially as indicated (Fig. 5).

The parametrial fixation stitches are next placed and include on each side, the parametrial tissue just lateral to the transfixed uteropubic ligaments. These are not tied until the anterior inversion stitch for the vaginal mucosa is placed (Fig. 6). Tying the fixation stitches unites the parametria in front of the remaining cervix, forcing it backward and anteflexing the corpus (Fig. 7). The cervical reconstruction is then completed by tying the anterior vaginal inversion stitch.

The remaining uteropubic fascia is then united in the midline, including the uterine tissue below the bladder level in order to lend further support to that structure. The vaginal mucosa is then trimmed and united in the midline (Fig. 8).

A perineorrhaphy is usually performed including reconstruction of the levator "sling," to add further support to the pelvic viscera.

The morbidity following this operation is unusually slight, and the great majority of temperature elevations was accounted for by urinary tract infections. Out of 51 patients, excluding urinary retention as a morbidity, 15 (or 29 per cent) developed morbid conditions as listed in Table II. There was no mortality. Fourteen

TABLE II. MORBIDITY IN 51 MANCHESTER OPERATIONS

	NO.	PER CENT
Cystitis	12	23.0
Pyelitis	8	15.0
Parametritis	2	3.0
Thrombophlebitis	1	1.9
Wound infection (perineum)	4	7.0
Secondary hemorrhage	1	1.9
Total Morbid Patients	15	29.0

patients had the Pezzar retention catheter inserted into the bladder following the operation for an average of five days. In this group there were 10 instances of cystitis and 8 of pyelitis. Twenty-eight of the remaining patients had to be catheterized more than once following the operation. There was one case of secondary hemorrhage from the cervix which occurred on the eighth postoperative day. This required ligation of a "spurter" and necessitated blood transfusion. The morbidity from the Manchester operation compares favorably with the morbidity following the two other operations most commonly used for prolapse and cystocele in our institution the past ten years. Vaginal hysterectomy was associated with a morbidity of 50 per cent and some of the conditions such as sepsis and peritonitis were major morbidities. The mortality from this operation was 1.7 per cent. The interposition operation had a gross morbidity of 40 per cent with no mortality (Table III).

TABLE III. COMPARISON OF OPERATIONS FOR PROLAPSUS UTERI

OPERATION	CASES	MORTALITY	MORBIDITY	CURES
*Vaginal hysterectomy	116	1.7%	50%	70.7%
*Interposition operation	30	0	40%	89.2%
Manchester operation	51	0	29%	97.9%

*Over ten-year period ending January, 1937 (Baer and Reis).

The pathologic findings in the amputated cervices revealed such conditions as old erosion, chronic endocervicitis, and Nabothian cysts. Two patients revealed squamous cell hyperplasia of the cervix and one a fibroma. The endometrial curettings were negative except for one case of old retained placenta (asymptomatic). Carcinoma was absent in all specimens.

The average stay in the hospital was twelve days. Eleven patients stayed over two weeks. Of these only 2 remained over eighteen days, one with parametritis, and one with a complete breakdown of the perineal wound.

The *results* of the operation were uniformly gratifying. All but 2 patients were followed. The period of follow-up postoperatively was as follows: 8 patients examined after twenty-four months; 13 patients examined between eighteen and twenty-four months; 8 patients between twelve and eighteen months; 15 patients between six and twelve months; and 5 patients between four and six months. A patient was declared to have a good anatomic result if the cervical stump was fixed high in the vault of the vagina; if the corpus uteri was anteflexed; and if there was no prolapse of the anterior vaginal wall. With these as criteria, the prolapse was cured in the entire series with but one exception (97.9 per cent cures). This was in a 54-year-old para v, who entered the hospital with a second-degree prolapse, large cystocele and rectocele and lacerated perineum. Her convalescence was uneventful. Fourteen months postoperatively, the cervical stump descended to the level of the ischial spines and was associated with recurrent cystocele. Salmon reported a series of 254 operations with one case of recurrent prolapse. Four of the 49 followed cases had recurrent cystocele. Since 46 of the followed cases had bladder operations, this represents an anatomic failure of anterior colporrhapy in 8.7 per cent of the cases. Stricture of the remaining cervical canal was encountered in 2 patients, and this was easily overcome by probing with a uterine sound.

The symptomatic cure was extremely satisfactory. All the patients were relieved of the "bearing down" sensation which was the most common preoperative complaint. The failure to completely cure the symptom of impairment ("stress" incontinence) was manifested in about one-third of the patients who originally complained of this symptom. However, the degree of control was markedly improved in the large majority of these patients.

Pregnancy following the Manchester operation has been reported rather frequently. In 1921, Fothergill, publishing the results obtained in 156 cases, reported two patients who had borne full-term children since the operation. His percentage of cures of prolapse in this series was 97 per cent. Shaw, reporting a large series of cases from the same clinic, cites 18 patients who had borne children subsequent to the operation. Of these 18, 5 or 27.8 per cent, developed a recurrence of the prolapse. These failures were not charged against the operation as they were considered due to a recurrence of the damage which produced the original prolapse. Salmon reports 2 patients who had uncomplicated labors, following the operation. There was no recurrence of prolapse or cystocele in either patient.

One patient in our series became pregnant one year after the operation. She was a para iv who had had quick labors previously, but the duration of the first stage in this labor was eighteen hours. The delivery was spontaneous, but complicated by a second-degree laceration of the perineum. Postnatal examination six weeks after delivery revealed a recurrent cystocele, but the uterus remained high.

Sterilization was performed in 4 of the 51 patients. In 3, the Madlener technique was used and in one cornual excision was done. Since the average age of our patients was 43, the necessity for sterilization was not frequently considered. In young women with large families, sterilization is a wise and often welcome additional procedure.

CONCLUSIONS

1. The Manchester operation is the best method of treatment for prolapse and cystocele in the large majority of patients, young or old.

2. The technique is readily acquired and is both anatomically and physiologically sound.

3. A cure of 97.9 per cent in prolapse by use of this operation definitely establishes its superiority over other methods of operative treatment.

4. The morbidity is low and is usually confined to urinary tract infection. There is no mortality.

5. The operation does not preclude future pregnancy and labor.

6. A modification of the original Manchester technique is described.

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58 EAST WASHINGTON STREET

DISCUSSION

DR. W. C. DANFORTH.—The procedure which has been described by the essayists for the cure of descensus of the uterus and bladder depends upon the reconstruction of the damaged upper pelvic floor, a name which was given many years ago by Polk to the structures at the level of the upper part of the cervix or lower part of the corpus which support the weight of the uterus. The ligaments of Mackenrodt, the uterosacral ligaments and the pubocervical ligaments or fascia are the more important parts of this structure. Between these ligaments is a network of fascial or connective tissue fibers, the whole making up an upper pelvic floor of which the ligaments just named are merely thickened portions. Injury at this level permits the uterus to descend or allows the bladder to herniate. When injury of the posterior part of the structure has taken place an enterocele follows. Repair of cystocele requires the reconstruction of the anterior part of this supporting mechanism. A true enterocele is not benefited by a repair of the perineum and is only cured by the repair of the posterior part of the upper pelvic floor.

Moderate degrees of descensus have been treated in some American clinics for years by detaching the bases of the broad ligaments and uniting them in front of the upper part of the cervix, with or without amputation of the cervix. This is an effective procedure. The proper restoration of the essential supports of the uterus and neighboring structures should result in relief of the descensus. Reported results from the clinic in which the operation originated as well as others from clinics elsewhere indicate that clinical experience bears this out. We must, therefore, include the parametrial fixation among the operations which may be used for the correction of descensus.

Abdominal operations are very rarely used at present in the treatment of descensus in gynecologic clinics and remain only as a means of treatment in the hands of occasional operators and of some general surgeons. Among the vaginal operations preferences will vary. The results reported in this paper are excellent both as to mortality and morbidity.

In our service we have continued to favor vaginal hysterectomy in our management of marked descensus. I am reporting 90 such cases in a series of 266 vaginal hysterectomies not yet published. In this group three recurrences have been seen, a rather larger incidence of failure than that reported by Drs. Leventhal and Boshes. In our experience, if a marked descensus is present, a considerable part or all of the uterus protruding from the introitus, we frequently find a marked enterocele. Often an important part of the operation is the excision of the pouch of Douglas and the approximation of the uterosacral ligaments in order to close the posterior portion of the upper pelvic floor. In studying the illustrations shown us by Drs. Leventhal

and Boshes I do not find that any part of their operation is devoted to the reconstruction of the posterior structures and this is true of other published reports. I do not find, in the tabulations, any note of enterocele; yet, in any considerable number of cases of marked descensus, the occurrence of this lesion would be expected. I would like to ask whether enterocele was a frequent finding and what the opinion is, in the Michael Reese Clinic, as to the necessity of surgical attention for its correction. In an illustration of an early stage of the operation a significant bulge is seen in the posterior vault which would indicate that the very skillful artist who made the drawings had noticed, or had had her attention drawn to, a more than normal fullness in that area. May I ask whether the support attained by the procedure described is sufficient in all cases to care for any posterior weakness? The colpoperineorrhapy which accompanies the parametrial fixation will, of course, help in controlling this by the aid it gives in keeping the uterus in anteversion.

The procedure described for the management of the vesical herniation is excellent and the description of the anatomical supports of the bladder is well given. Familiarity with these supports and a knowledge of the mechanism of bladder herniation are essential for effective correction of descensus of the organ. The emphasis which is placed upon the freeing of the bladder at each side before displacing it upwards is wise. This is important in all operations in which the bladder is raised to a higher level. Failure to mobilize the bladder laterally will not only endanger the ureters, as the essayists point out, but may cause the bladder, after operation, to assume a "saddle bag" shape.

The risk of this operation should, as the essayists say, be less than that of the other available means of surgically treating descensus. This fact, together with the very good results which the operation has given in the hands of the staff of the clinic from which this report comes, must cause us all at least to consider parametrial fixation as one of the procedures available for the management of descensus.

DR. N. S. HEANEY.—I like this operation as described tonight very much for cases of marked cystocele and rectocele. I see no need, however, to call this a Manchester operation as all of the Manchester part has been replaced by better procedures, particularly by the step of the bladder advancement. The type of operation to choose in a prolapse depends upon the sort of case which is confronting one. This operation is a good one if the uterus does not protrude beyond the introitus and where a marked cystocele is present. This operation has no place, however, in the treatment of complete procidentia. If a case of procidentia is to be cured by a vaginal operation, the uterus has to be removed so as to get a high anchorage on the ligaments of the uterus for the vagina. The interposition has no place in the treatment of any sort of prolapse or cystocele.

DR. JOSEPH L. BAER.—Twenty per cent of all women normally have a retrodisplacement. The work of Sturmdorff in his studies of pelvic inclination convinces me that this plays a role in the appearance of so-called normal retrodisplacements. Now if that group of young women who first come under our observation with so-called normal retrodisplacement could be followed through into their maturity and middle life, I believe that a goodly proportion of prolapse would be found to arise out of that group of normal retrodisplacements. Occasionally but very rarely we find prolapse with anteflexed or anteverted uterus, but so seldom do we find it that I must protest against ignoring the effect of intra-abdominal pressure in the production of retrodisplacement and its sequela, descensus uteri.

DR. LEVENTHAL (closing).—Occasionally either advertently or inadvertently we open into the cul-de-sac of Douglas and when this is done the cul-de-sac is closed by a purse-string high on the uterine wall.

The interposition operation, we believe, has a definite place in the treatment of prolapse. It is especially valuable in cases of huge cystocele, the corpus uteri acting as a support for the bladder. We have noticed time and again in patients with cystoceles and incontinence that by putting two fingers in the vagina they are able to control the act of urination. The corpus of the uterus acts as a permanent support in these cases, and thus interposition with cervical amputation is a valuable procedure.

THE INFLUENCE OF THE HORMONAL ACTIVITY OF THE OVARIES UPON THE CHARACTER OF TUBAL CONTRACTIONS AS DETERMINED BY UTERINE INSUFFLATION*

A Clinical Study

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THE possibility of estimating ovarian function clinically by the character of the rhythmic tubal contractions was suggested in 1927.[1] This assumption was based upon experimental facts and upon observations made with the test for tubal patency. Experimental and histologic studies of Kehrer,[2] Blair,[3] Corner,[4] R. T. Frank,[5] S. R. M. Reynolds,[6] Seckinger and Snyder,[7] Wislocki and Guttmacher,[8] Westman,[9] Manzi,[10] Moir,[11] Andersen,[12] Moreau[13] and Lee[14] and many others have indicated a close correlation between cyclic functional and anatomic changes in the tubes and synchronous processes in the ovary. The material used in these studies consisted in most instances of isolated portions of the Fallopian tube or the whole tube of various species including the monkey. The excised organs were kept in a state of temporary survival.

Rhythmic contractions of extirpated oviducts of the sow have been demonstrated by insufflating oxygen through the attached uterus, while the organs were immersed in Locke's solution at body temperature (I. C. Rubin,[1] Whitelaw[16]). The pressure variations were thus recorded as well as the rhythmicity of the contraction waves. Mikulicz-Radecki[15] repeated my experiments and found similar results. In order to see whether there is a similarity between the rate of contractions of the intact oviducts and that of segmented portions, Whitelaw[16] undertook the task of insufflating the uterus and Fallopian tubes of the sow after the manner employed clinically. As the ovaries were available, the particular estral phase could be determined. He found that in most specimens the uterotubal junction during estrus resisted the passage of oxygen to a pressure of 200 mm. Hg. This resistance was due to the presence of hypertrophied lymphatics and valve-like folds of the mucosa which were situated at the uterine ostia of the tubes. In a few specimens not presenting these obstructions the gas entered the tubes at a pressure of 20 mm. Hg; the manometric fluctuations were uniform in rhythm and amplitude and averaged fifteen to the minute, a rate which was identical with the rate of muscle strip contractions during estrus.

During diestrus there was a marked irregularity in the character of the contractions; the two tubes from the same animal showed no similarity and the initial rise in pressure varied from 40 to 100 mm. Hg. There was no correspondence between the number of contractions as exhibited by isolated tube segments and by the intact tubes.

Uterotubal insufflation in the living monkey was undertaken by Morse and Rubin[17] with the view of studying the relation between uterine and

*An abstract of this paper was presented at the International Congress of Obstetrics and Gynecology, May 6, 1938, at Amsterdam, Holland. The material contained therein was used in discussion of the paper by Geist, Salmon and Mintz on the "Effects of Estrogenic Hormone on the Fallopian Tubes," presented at the New York Obstetrical Society, October 12, 1937 and published in the issue of July, 1938 (page 67) of the JOURNAL.

tubal contractions and the menstrual ovulation cycle, and of establishing some graphic pattern which could be taken as evidence of ovulation. In respect to the latter, this work has reached only the preliminary stage, a method of approach being the first task to be accomplished. Intravenous injection of oxytocic and hormonal extracts have produced definite effects upon the intact uterus and tubes. The results so far obtained in the monkey have encouraged a similar clinical study.

Seckinger and Snyder[7] were the first to study the cyclic changes in *extirpated human* Fallopian tubes by noting the contractions of isolated rings of muscle at various times of the menstrual cycle. They found that during the premenstrual phase the tubal contractions were of uniform amplitude but slower, about 4 per minute. More rapid contractions were found at the early interval stage while at the midinterval the contractions were rapidly increased in rate occurring at about 8 per minute and showing a striking variation in amplitude. In two of the latter showing 8 contractions per minute, it was possible for these observers to check the status of the ovary by laparotomy. In one case, an ovary showed a corpus luteum without signs of regression and in the other there was a recently collapsed follicle.

Intact temporarily surviving extirpated human Fallopian tubes also manifest rhythmic contractions when oxygen is insufflated through them, as I have had occasion to demonstrate a number of times. These motions are similar to those exhibited by living tubes in situ, a fact which was recognized in 1920 in the early experience with uterine insufflation. The human uterus, as far as we know, contains no anatomic structures at the tubal junctions resembling either the lymphatic apparatus or valve-like folds of mucous membrane which almost invariably hypertrophies at estrus in the lower animals that have been studied so far. This lymphatic apparatus offers a resistance to the passage of insufflated gases or injected fluids.

If ovulation in women is accompanied by definite changes in the rate of tubal contractions or other significant changes comparable to the results obtained in physiologic experiments on the isolated organs, it is conceivable that insufflation could serve as a method of identifying this event clinically. The search for a simple method appears to be all the more warranted because the only direct proof of ovulation is obtained by recovering ova from the Fallopian tubes as was done by Newell, Allen, Pratt and Bland.[18] The time of ovulation can be approximately estimated by inspection of the corpus luteum. But as this requires a laparotomy, one is obliged to depend upon such indirect evidence as can be obtained by (1) histologic examination of the vaginal secretions; (2) endometrial biopsy and (3) biologic assays of the estrin content of blood and urine. Although time consuming, such quantitative determinations of estrogenic substances justify further efforts. Whether in conjunction with other criteria, which was recommended as desirable in 1928,[19] or whether employed alone, it has seemed worth while to explore the possibility of using insufflation as another objective method of hormonal assay.

The routine performance of tubal insufflation as a test of tubal patency in women has brought out certain changes in the pattern of tubal contractions that appeared to me to bear a time relationship to the menstrual cycle. However, this impression was based upon random observations

in no definitely planned group of cases. In a paper published in 1928 on tubal patency it was stated that "there was not the same uniformity in the clinical cases which has been established by the muscle strip experiments in the lower animals." It was felt that "further observations along this line must be made in conjunction with parallel investigations that may be carried out in estimating the quantity of female sex hormone, etc. Whether the female sex hormone will prove responsible for activating the uterine mucosa and also tubal peristalsis at the same time, by increasing and decreasing quantities poured into the blood stream or through the follicle fluids directly into the oviduct remains to be determined."[19]

Though the parallel investigations suggested by me on the same group of patients whose tubal function was determined by insufflation were not undertaken, great strides were made in the estimation of estrogenic hormones.

The reasons for the random observations were twofold: (1) Since the primary object of insufflation was to test for tubal patency, the vast majority of patients were examined during the week following menstruation. (2) As the restoration of fertility was much desired, it was not deemed advisable to insufflate at other times of the menstrual cycle when the tubes might contain an impregnated ovum. Although the mechanical displacement of a tubal ovum may be regarded as hypothetical, the use of insufflation at other phases of the menstrual cycle was, nevertheless, limited prior to 1928 to those women who had had no coital relations for two weeks or more from the onset of the last regular menstruation. Additional data have been collated in the past ten years from a selected group of patients in whom for special reasons an insufflation was performed on days outside of the postmenstrual phase, their menstrual habit being regular and normal.

A fairly large group of patients whose menstruation was habitually delayed and a smaller group of cases of amenorrhea were available, serving the purpose of comparison. An analytical study was made of any striking variations in relation to the menstrual cycle which might be properly considered as characteristic of the ovulation phenomenon particularly and of ovarian function in general. A small number of menopausal cases and a larger group of artificial castrates were examined to get an idea of what degree of tubal function may be found when the ovaries are functionally or structurally ablated. In addition, a study has been made of a small group of women with frequent and profuse menses. In most instances the length of time consumed by the insufflation was from three to five minutes. In a smaller number the test was prolonged twice and three times. Several of the amenorrheic patients were treated with progynon injections and the effect upon the tubes as determined by insufflation was noted.

Results

A. Tubal contractions in women whose menstrual habit was regular

There were in my series 100 women with normal tubal patency and normal menstrual cycles who were suitable for insufflation from the tenth to the sixteenth day of the cycle counting from the first day of the preceding menses. An equal number

were also insufflated from the sixteenth to the twenty-eighth day of the cycle. These two groups were compared to an equal number of a third group taken in sequence from the large series of patients tested for tubal patency between the seventh and the tenth day. The ages of the patients in the three groups were similar, from twenty to thirty-five years and the total number aggregated 300.

Several points were particularly noted during the insufflation:

1. *Initial Rise of Pressure.*—The pressure at which gas passed the uterotubal junction was taken to indicate uterotubal tone. In general, the patients who were insufflated during the tenth to the sixteenth day of the menstrual cycle required higher pressures, twice as often as the patients in the two other groups.

2. *Rate of Tubal Contractions.*—The number of contractions per minute was noted in the three groups. The contraction rate showed a tendency to be increased in the patients insufflated from the tenth to the sixteenth day of the cycle (Fig. 1). Thus 21 patients (21 per cent) of the tenth- to the sixteenth-day group had 7 to 9 contractions as compared to 8 patients (8 per cent) of the seventh- to tenth-day group, and 16 patients (16 per cent) of the sixteenth- to twenty-eighth-day group. The

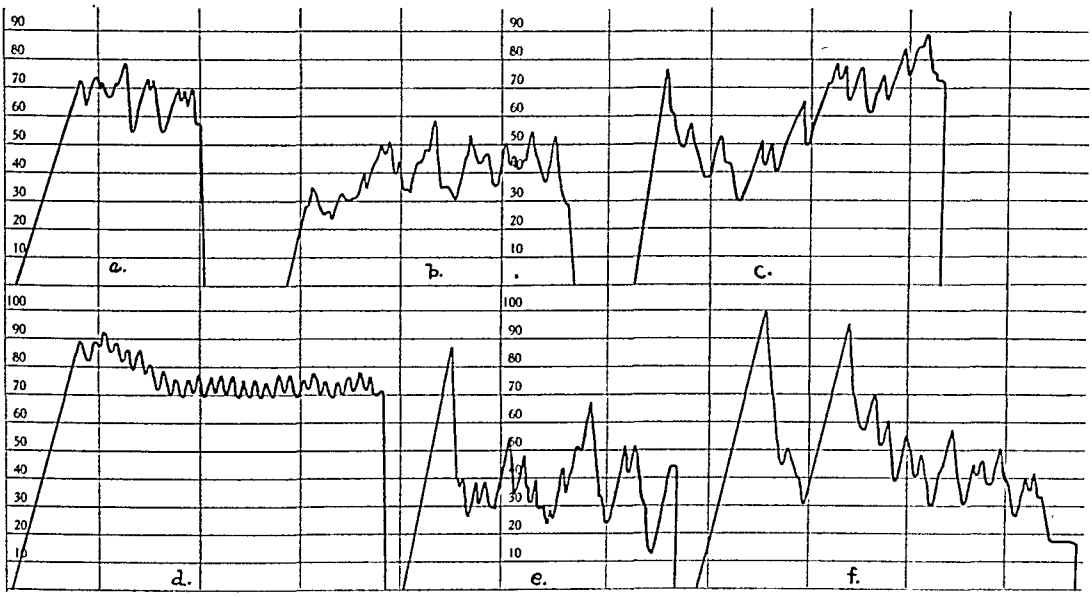


Fig. 1.—Insufflation at various intervals of the menstrual cycle: (*a*) Sixth day of cycle; (*b*) seventh day of cycle; (*c*) ninth day of cycle; (*d*) twelve day of cycle; (*e*) eighteenth day of cycle; (*f*) twenty-third day of cycle.

rest of the patients had less than 7 contractions per minute. In human tubes an increased contraction rate appears to be demonstrated during the period when ovulation is theoretically supposed to take place. On the other hand the presence of more frequent contractions during the other phases of the menstrual cycle suggest the possibility of ovulation taking place in women without the predictable regularity met with in lower animals. The overlapping in the three groups points to the possible shifting to a certain extent of the day of ovulation away from the fourteenth day.

3. *Amplitude of Tubal Contractions.*—The maximum range in amplitude of tubal contractions was noted in the three groups. The contractions ranged between 15 and 50 mm. Hg in 70 patients (70 per cent) of the seventh- to tenth-day group as compared to 71 (71 per cent) of the tenth to sixteenth-day group, and 73 (73 per cent) of the sixteenth- to twenty-eighth-day group. The remainder had maximum contractions of less than 15 mm. Hg. In many of the cases insufflated from the tenth to the sixteenth day of the cycle, shallow contractions were infrequent. Most of the fluctuations during this menstrual interval were of the maximum range and of perfect rhythm. In the two other menstrual phases contractions with the maximum range were few in comparison to the more shallow types.

B. TUBAL CONTRACTIONS IN WOMEN WITH HABITUALLY DELAYED, SCANTY OR ABSENT MENSES

Study of the possible hormonal influence upon the tubes was extended to instances of delayed menstrual periods in a group of women of the reproductive age. The patients studied had menstrual periods that were habitually delayed at least two weeks. Many had from 2 to 6 menstrual periods per year. Observations were made by means of insufflation and the kymograph upon tonicity, and upon the rate and amplitude of tubal contractions. Long-standing amenorrhea showed, in general, greater changes than did slight menstrual delay. No differences were noted between hypomenorrhea, oligomenorrhea, or hypo-oligomenorrhea.

There were 198 out of a series of 770 patients with habitually delayed periods who had normal tubal patency. As the kymograph was not used in 56 of these (early) cases, 142 remain of whom the findings can serve as a comparison with the normally menstruating group. The ages of the patients in the comparative groups were similar, ranging from 20 to 35 years.

Twenty patients had prolonged amenorrhea. In 9 of these the amenorrhea was of one or two years' duration; in 6 from 3 to 5 years; 2 of 6 years' duration; one patient had not menstruated for 8 years, and 2 patients for 14 years.

The remaining 122 patients were insufflated at the following intervals after their menses: in the first week 42; in the second week 32; in the third week 7; in the fourth week 7; in the second month 8; in the third month 11; in the fourth month 3; in the fifth month 2; in the sixth month 2; in the seventh month 4; in the eighth month 3; and in the ninth month 1.

The findings were as follows:

Initial Rise of Pressure.—The initial rise of pressure, i.e., the point at which the gas passed through the uterotubal junction, was strikingly lower in the patients of this group. Forty-four (30.9 per cent) had pressures between 20 and 50 mm. Hg as compared to 17 patients (11.9 per cent) of those with normal periods. Thirty-nine patients (27.5 per cent) of the group with hypo-ovarian function had pressures above 80 mm. Hg as compared to 45 patients (31.7 per cent) of those with normal periods. The rest of the patients had pressures between 50 and 80 mm. Hg.

Of the 20 patients with long periods of amenorrhea, 9 (45 per cent) had initial pressures under 50 mm. Hg; 10 (50 per cent) had pressures between 50 and 80 mm. Hg, and only 1 (5 per cent) had an initial pressure over 80 mm. Hg.

If the initial rise of pressure may be taken as an index of uterotubal tonicity, it would seem that it corresponds to the degree of ovarian hypofunction, i.e., the more pronounced the latter, the lower the uterotubal muscle tone.

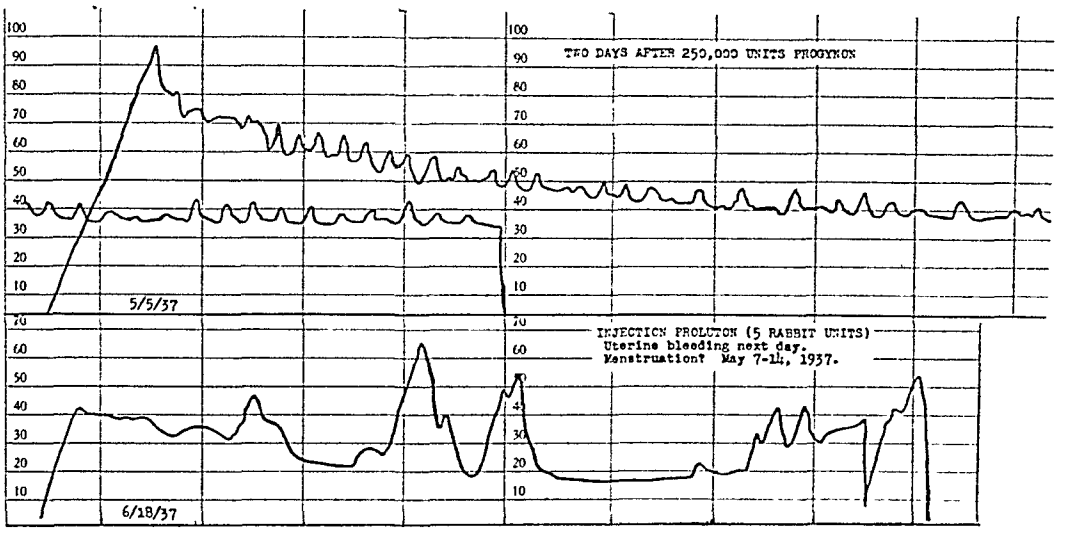
Contraction Rate.—There was a reduced contraction rate in the women with habitually delayed, scanty, and absent menses. Thus 92 cases (64.8 per cent) had 3 or less contractions per minute (7 had no tubal contractions) as compared to 31 cases (21.8 per cent) of the patients with normal periods. Only 12 patients (8.5 per cent) had more than six contractions per minute. This percentage was slightly less than that which obtained in the women with normal menstrual periods (12.7 per cent).

Exceptionally, hypertonicity was associated with amenorrhea. Whenever this was encountered it was felt that possibly the insufflation happened to be done at a phase of heightened follicle activity. Follow-up notes are lacking as to the occurrence of the next menstruation in these particular cases. The determination of the approximate time of ovulation in cases of habitually delayed menstruation, if feasible, would have the practical value of enabling us to predict the onset of labor in such cases with a greater degree of probability.

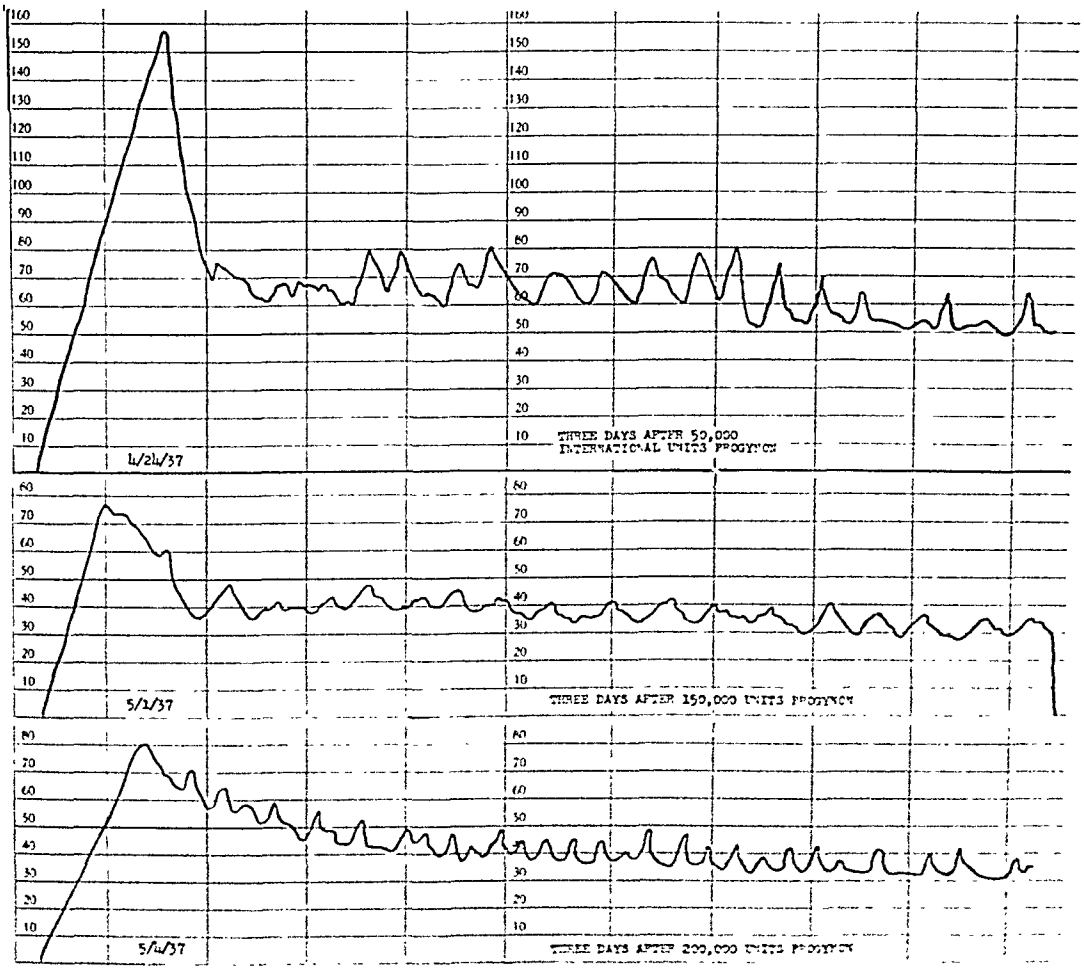
Judging from observations on the rate of contractions the latter appears to depend upon the degree of ovarian hypofunction. Thus of the 20 cases of long standing amenorrhea, 10 (50 per cent) had 3 or less contractions and only 2 (10 per cent) had 5 or more contractions per minute. These two cases may have been in or near the ovulation phase when the insufflation was done. One of the patients with an amenorrhea of fifteen months menstruated four months after the test, another with an amenorrhea of one year menstruated two months later. Two patients with amenorrhea of six to eight months menstruated within three weeks of the test. One other

having received large doses of progynon bled seven days after the injections were completed (Fig. 2, *A*, and *B*).

Range of the Contractions.—In the group of patients with scanty, delayed or absent menses, strong contractions were rare. Usually there were weak contractions



A.



B.

Fig. 2.—*A* and *B*. Effects of progynon injections on tubal contractions. Showing increased rhythmicity and higher uterotubal tonicity.

having an amplitude of 10 mm. Hg or less. Thus a frequent finding was one strong contraction to several weak contractions during an insufflation lasting three or more minutes.

Fatigability of the Tubes.—In 21 of the 142 cases with habitually delayed or absent periods, the tubes manifested fatigability by a decrease in the number and depth of contractions which occurred after a minute or two or longer (Fig. 3). Had the test been prolonged the incidence of fatigability might have been much higher. Fatigue occurred after one minute in 7 cases, after two minutes in 10 cases, after three minutes in 3 cases, and after four minutes in 1 case.

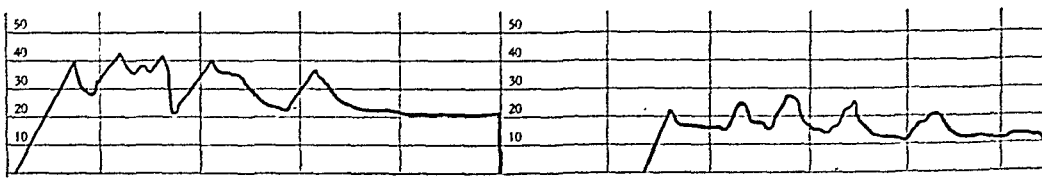


Fig. 3.—Graphs showing low initial pressures, poor tone, and fatigability as evidenced by loss of contractions after three minutes of insufflation.

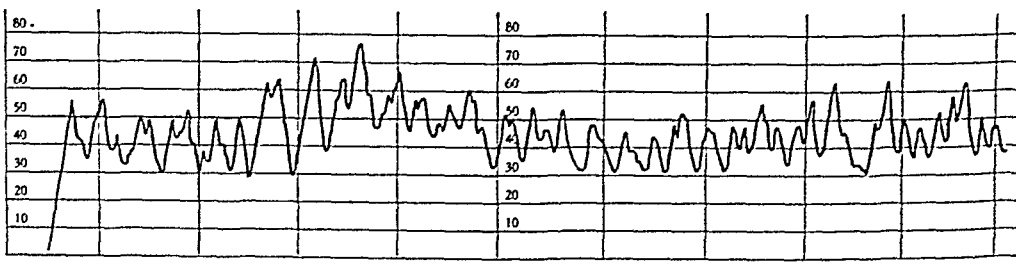


Fig. 4.—Rhythmic contractions in normal tubal patency with normal menstrual cycle. Note continuation of rhythmic contractions for ten minutes. This patient was insufflated for forty minutes in order to produce a large pneumoperitoneum. The contractions persisted throughout the insufflation.

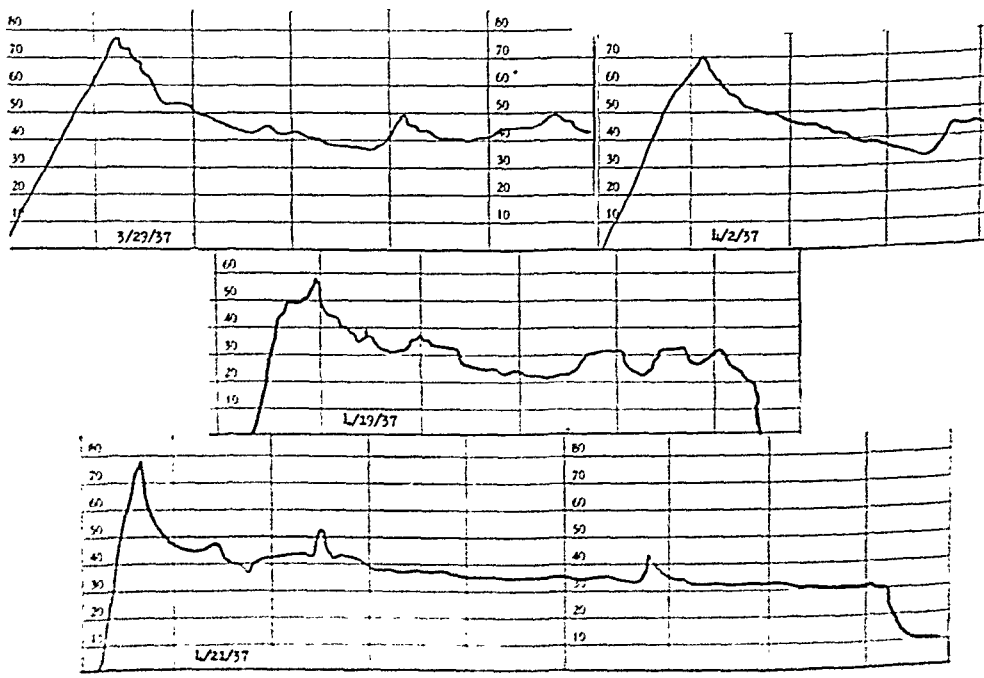


Fig. 5.—Insufflation at three day intervals in a patient with spontaneous secondary prolonged amenorrhea. Same patient as in Fig. 2, *A* and *B*.

This is a striking departure from the normal. In women with a normal habit of menstruation, the rhythmic contractions continue practically in a uniform way as long as the gas is permitted to flow through the tubes, at least for two to fifteen minutes (Fig. 4).

Cyclic Variation Demonstrated by Repeated Tests.—In 22 of the cases of amenorrhea, repeated tests were done, four at weekly intervals or oftener to note differences in the insufflation curve which might correspond to a cyclical pattern (Figs. 5 and 6). With the exception of two cases, the insufflation findings suggested such cyclical rhythm both with regard to the number of contractions per minute and the degree of tonicity. In one, the amenorrhea was of seven years' duration; insufflation was performed at weekly intervals. There appeared to be a cyclic change as demonstrated by a corresponding variation in the number, in the amplitude of contractions and to a less degree in the initial rise of pressure (tonicity).

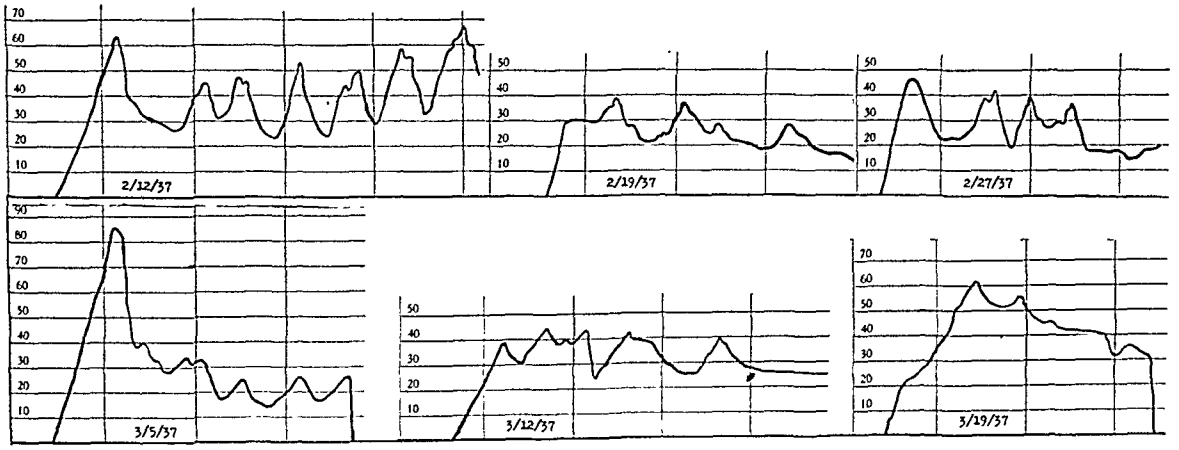


Fig. 6.—Insufflation at weekly intervals. Same patient as in Fig. 2, *A* and *B*.

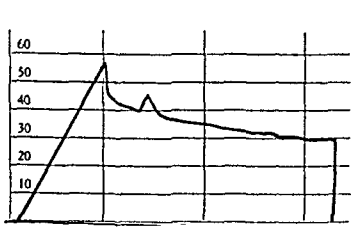


Fig. 7.

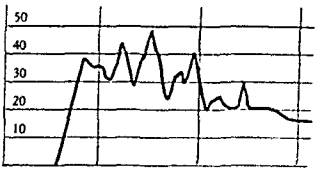


Fig. 8.

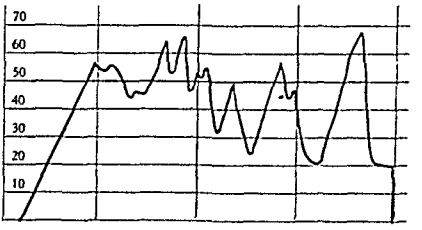


Fig. 9.

Fig. 7.—Insufflation of patient 55 years old; menopause of nine years' duration. Note absence of tubal contractions.

Fig. 8.—Insufflation of patient following x-ray abortion (castration dose). Graph shows a low pressure level and tendency to fatigability (absence of contractions) after two minutes.

Fig. 9.—Patient with menorrhagia insufflated at seventeenth day of cycle. Note deep strong tubal contractions.

Tubal Contractions in the Menopause.—Insufflation was performed in 9 women at the menopause, ranging in age from 40 to 49, in whom menstruation had ceased from three months to nine years. In all 9 there were a low initial pressure rise and infrequent shallow or absent fluctuations (Fig. 7). The initial rise of pressure at which the gas passed the uterotubal junction varied from 25 mm. Hg to 80 mm. Hg; 5 of the patients having an initial pressure rise below 50 mm. Hg. In 4 patients there were no tubal contractions whatever; in the remainder the contractions were infrequent and rarely reached a depth above 5 mm. Hg. The uniformity of these findings would appear to correspond with the lowered or absent hormonal output of the ovaries during the menopause. It need only be mentioned that deductions can be made only when the tubes are freely patent; when obstructed the initial pressure is, naturally, high.

Effect of "Stimulating" Doses of X-ray and Radium on Tubal Contractions.—In five cases with delayed periods (ovarian hypofunction), the tubes were insufflated both before and after treatment with "stimulating" doses of x-ray or radium. There was no appreciable effect upon the initial rise of pressure. In all 5 there was an increase in the contraction rate. Of 2 patients who exhibited no contractions before x-ray stimulation, one had 3 contractions after treatment and the other 5 contractions per minute. The depth of contractions was also increased; in one to a range of 5 to 20 mm. Hg and in the other it fluctuated round about 5 mm. Hg.

Effect of X-ray Castration on the Tubes (Dosage for the Induction of Abortion).—The effect of x-ray castration on the tubes was studied in 33 women who had had a therapeutic abortion by x-ray. As these women were all still in the reproductive period, their tubes being normal, they afforded an exceptional opportunity to study the contraction curves as determined by uterotubal insufflation (Fig. 8).

Twenty-two patients, or 66.6 per cent of the group, had initial pressure rises under 50 mm. Hg, as compared to 11.9 per cent of patients with a normal menstrual cycle. Only 2, or 6.1 per cent, had pressures above 80 mm. Hg, as compared to 31.7 per cent of the group with normal menstrual cycle. Nine patients, or 27.3 per cent, had pressures from 50 to 80 mm. Hg.

An actual increase in the number of contractions was seen at the onset of the insufflation in a third of this group. But after the first minute or two the oscillations were only occasional, or altogether absent showing definite signs of fatigue. Moreover, though they were occasionally as well marked as in cases with normal menstrual function the weaker contractions were generally more conspicuous.

C. TUBAL CONTRACTIONS IN WOMEN WITH FREQUENT AND PROFUSE MENSES

A further study of the possible hormonal influence upon the tubes was made in a group of 29 women with profuse and frequent periods. In a group of 156 cases of sterility associated with profuse and frequent periods only these 29 (18.6 per cent) had normal tubal patency (Fig. 9).

Initial Rise of Pressure.—The point at which the gas passed through the uterotubal junction, was markedly higher in the patients of this group. Only 1 (3.4 per cent) had a pressure below 50 mm. Hg as compared to 30.9 per cent of the larger group with delayed and scanty periods, and 11.9 per cent of those with normal periods. Nineteen (65.5 per cent) of the group with frequent and profuse periods had initial pressures above 80 mm. Hg as compared to 27.5 per cent of the group with hypo-ovarian function and 31.7 per cent of those with normal periods. The rest of the group had pressures between 50 and 80 mm. Hg.

These findings would seem further to substantiate the belief that the tonicity and initial pressure are proportional to the degree of ovarian function.

Contraction Rate.—The contraction rate in women with profuse and frequent menses maintained a midway course between the group of women with delayed and scanty periods and those with normal menses. Thus, 29 (44.4 per cent) had 3 or less contractions as compared to 64.8 per cent of the group with delayed and scanty periods and 21.8 per cent of the patients with normal periods. Only 1 (3.4 per cent) had more than six contractions.

Range of the Contractions.—The range of contractions in women with frequent and profuse periods was less than that of women with normal periods, and exceeded that of women who had habitually delayed and scanty periods. Thus, 18 (62.1 per cent) had contractions with a range of 15 to 50 mm. Hg as compared to 71.3 per cent of the patients with normal periods, and the rare case in the group with delayed and scanty periods. The remaining 11 cases (37.9 per cent) had contractions under 15 mm. Hg.

SUMMARY

The character of tubal contractions as elicited by uterotubal insufflation was studied in relation to the type of menstruation in 513 patients with tubal patency. The patients with normal menstruation were

divided into three groups: (1) those who were insufflated from the seventh to the tenth day, counting from the first day of the menses; (2) those between the tenth and sixteenth days, and (3) those between the sixteenth and twenty-eighth days. Because of the greatest interest in identifying the event of ovulation, which is said to occur between the tenth and sixteenth day of the menstrual cycle, more than half of the cases fell into Group 2, totaling 300. These three groups were compared to each other and also served as a comparison for patients with abnormal menstrual cycles.

There were 142 patients with habitually delayed menses, 20 with prolonged spontaneous amenorrhea, and 33 who had been subjected to x-ray castration for the purpose of inducing abortion. There were 5 women in this series who had been subjected to treatment by so-called stimulating doses of x-rays to regulate the menses. Nine women who had entered the menopause had their tubes insufflated for comparative purposes. In addition, tubal contractions were studied in a group of 20 women with frequent and profuse periods.

The results of this study have shown that:

A. In general the tubes in patients with normal menstrual cycles exhibit during insufflation uniform contractions and relaxations varying in rate between 3:4 to 8:9 per minute; the less frequent rate coinciding with the anovulation phase (7:10 and 16:28 days); the more frequent rate of contractions with the ovulation phase (10:16 days). The tonicity of the tubes is moreover somewhat greater during the ovulation phase as evidenced by deeper ranges of pressure fluctuations.

B. In the patients with habitually delayed menses the uterotubal tone is in general lowered and the contraction relaxation rate less frequent per minute except when insufflation happens as it appears to coincide with a possible ovulation phase.

C. In the group of cases of spontaneous prolonged amenorrhea occurring during the reproductive period, uterotubal tone, frequency and range of tubal contractions are as a rule decreased, although a cyclical variation may be demonstrated in a number of them. In the amenorrhea of menopause, uterotubal tone, contraction rate and amplitude are all markedly diminished, contractions being frequently absent.

D. In x-ray castration during the reproductive period, a certain cyclical pattern is frequently maintained but the tonicity and frequency of contractions are relatively diminished.

In the cases where so-called stimulating doses of x-ray were used, the effects upon the contraction rate and amplitude are augmented.

E. In the cases of frequent and prolonged menses, uterotubal tone, contraction rate and amplitude are less than in patients with normal periods and more than the group with habitually delayed and scanty menses.

There appears to be a definite correlation between the character of tubal contractions as elicited by tubal insufflation and the menstrual function. Since the menses depend in the main upon ovarian function, whether this be primary or subordinated to the pituitary or other inner secretory glands, it follows that absence of menses or depressed menses

may be assumed to be due to under-function of the ovaries. As tubal contractions are influenced by the hormonal action of the ovaries, any deviation from the normal may therefore be reflected in the pattern of tubal contractions. This appears to be susceptible of clinical assay and demonstration by uterotubal insufflation. In a few cases of prolonged secondary amenorrhea systematic injection of progynon was carried out. A dynamic effect upon the tubes appeared to be demonstrated (note Fig. 2). Where there had been shallow or irregular and infrequent contractions prior to the progynon injections, they became regular, of increased amplitude and frequency after the injection.

In order to establish typical patterns corresponding to the ovulation phase, a greater number of cases will have to be examined by this method and paralleled by blood and urine estrogen determinations as well as histologic examination of uterine and vaginal biopsies. The method is limited to patients with normally patent Fallopian tubes. When the tubes are nonpatent the uterus may serve as the medium for this assay by the same method.*

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*Although easily carried out, as has been demonstrated a number of times in the female monkey and in women, my work has not progressed far enough to warrant deductions. It may only be noted that it can serve satisfactorily and is simple to carry out.

ROLE OF THE UTERUS IN THE PRODUCTION OF MANOMETRIC FLUCTUATIONS DURING UTEROTUBAL INSUFFLATION (RUBIN TEST)*

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SINCE Kehrer's[1] classic experiments with isolated strips of excised tube, numerous animal experiments have demonstrated the presence of tubal contractions and peristalsis. In May, 1925, Rubin[2] began the study of human tubal peristalsis by recording on a revolving drum the variations in pressure coincident with the passage of gas through the uterus and tubes.

Guthman[3] was the first to express the opinion that manometric fluctuations were due to tubal peristalsis. He based this conclusion on the well-known fact that when the tubes are closed, fluctuations are not observed on the manometer. Much experimental work was done to substantiate this contention. However, further evidence is necessary to determine whether or not the uterus participates in the production of manometric fluctuations during uterotubal insufflation, and if so, to what extent. To clarify this subject, these experiments have been carried out on the uterus and tubes of living rabbits, and on excised specimens.

MATERIAL AND METHOD

Experimental observations were made on the intact uteri and tubes of 60 mature rabbits, weighing from 2 to 4 kilograms. They were anesthetized by the intravenous injection of nembutal, 1 gr. to 2.2 kilograms. Further studies were made on the excised specimens suspended in oxygenated Locke solution.

Changes in manometric fluctuations during gas insufflation of the uterus and tubes were recorded on the kymograph of the Rubin apparatus.[4] Carbon dioxide gas under 15 pounds of pressure was employed at a constant rate of flow, one second being required for the passage of 1 c.c.

For the routine uterotubal insufflation, a bulb tipped medicine dropper or Keyes-Ultzman cannula was passed into the uterus through a small incision 2 cm. from the uterotubal junction, and tied tightly. For retrograde tubouterine insufflation, a needle cannula was tied in the fimbriated end of the tube. For uterine insufflation alone, the cannula was tied into a segment of uterus, the wall of which was punctured to allow the gas to escape through it and thus preventing it from passing through the uterotubal junction and tubes. For tubal insufflation alone, a needle cannula was passed through the uterotubal junction into the tube, and tied tightly.

In order to demonstrate focal contractions of the uterine and tubal muscle a small needle hook was passed through the entire thickness of muscle, down to the mucosa, and the contractions were recorded on a smoked drum.

TUBAL PATENCY NECESSARY FOR MANOMETRIC FLUCTUATIONS

During uterotubal insufflation, pressures of 50 to 200 mm. Hg were necessary in different rabbits to force the gas from the much wider uterine cavity through

*We are indebted to Dr. I. C. Rubin for the suggestion and supervision of these experiments.

the narrow uterotubal junction. Once the gas passed this narrow aperture, there was a drop in pressure and manometric fluctuations were recorded as long as the gas was allowed to pass through the tubes.

In 10 experiments in which gas failed to pass the uterotubal junction at pressures of 200 to 220 mm. Hg, there were no pressure fluctuations. In three experiments the tubes were patent to the gas and exhibited pressure oscillations as the gas flowed through them. When these tubes were clamped off the fluctuations ceased. When the pressure was released 10 mm. Hg at a time by means of a release valve down to the lowest pressure levels, no fluctuations were produced. However, when the clamps were removed from the tubes of these three rabbits, manometric oscillations appeared with visible peristalsis of the tubes. The pressure patterns were somewhat altered at first owing to the momentary injury, but they rapidly regained their previous undisturbed character.

Whenever the intrauterine pressure was below that which was required for the gas to pass the uterotubal junction, no manometric fluctuations occurred.

These experiments indicate that tubal patency must be present for the demonstration of manometric fluctuations during uterotubal insufflation.

COMPARISON OF INSUFFLATION OF THE UTERUS ALONE WITH UTEROTUBAL INSUFFLATION

In the undisturbed state the uterus and Fallopian tubes were seen to undergo rhythmic peristaltic movements. However, during uterotubal insufflation, the uterus

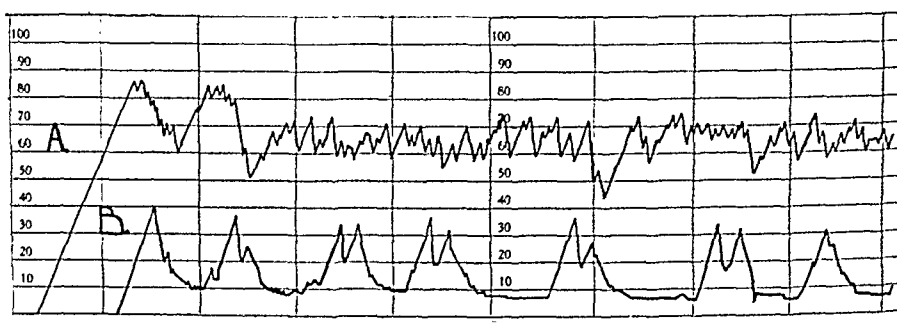


Fig. 1.—*A*, Uterotubal gas insufflation, showing numerous manometric fluctuations. *B*, Insufflation of solitary uterine segment, showing fewer and deeper manometric fluctuations at a lower pressure level.

became distended and remained so as long as the gas was allowed to pass through the tubes. This distended organ appeared inactive. Occasionally, as was noted in three rabbits, the gas passed the uterotubal junction at a low pressure without causing marked distention of the uterus, and weak uterine peristaltic movements were noted. Once distended, the uterus was found to lose its contractility temporarily, so that for comparison with uterotubal insufflation, a segment of uterus was insufflated which had not been subjected to previous distention. A segment of uterus 5 cm. in length was employed for this experiment, the tube being entirely excluded. Gas was allowed to escape through a small opening made in the uterine wall. The direction of the cannula in the uterus, toward or away from the vagina, had little effect on the findings.

In the phase of contraction the uterus or tube became shorter and thicker. During insufflation, the contractions appeared simultaneous with the upward rise of the mercury pressure and the upward stroke on the drum. During relaxation the pressure dropped. During the contraction gas would either fail to escape from the fimbria or the small opening in the uterus, or when it did pass through these points it came out in the gentlest stream of small bubbles. The moment the contraction ceased (relaxation phase) the gas at once escaped in large, rapidly succeeding bubbles.

In 30 experiments the contractions obtained by insufflating a solitary segment of uterus were entirely different from those of uterotubal insufflation (Fig. 1). The uterotubal junction acted as a barrier to the gas to a pressure far in excess to that which was necessary when the gas passed through the uterine opening. Thus, gas passed through the artificial uterine opening at pressures of 10 to 50 mm. Hg. The pressures required to force gas through the uterotubal junction to record tubal contractions varied from 50 to 200 mm. Hg, and correspondingly higher pressure levels were maintained as long as the gas was allowed to flow. When the uterus alone was insufflated, the rate of contractions was much less than when the tube was included.

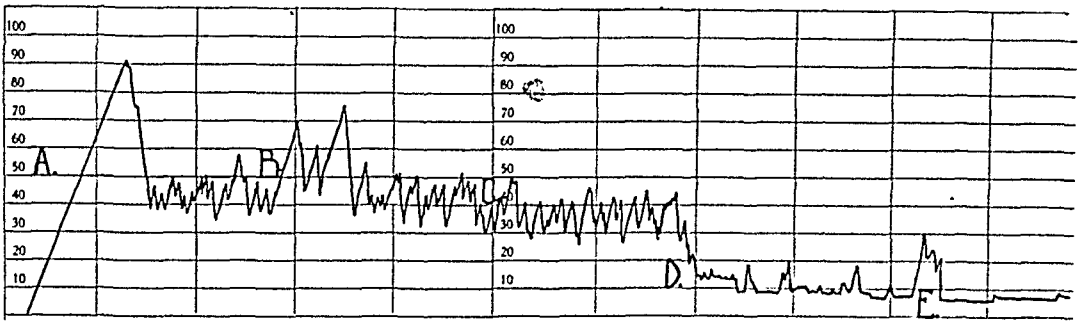


Fig. 2.—*A*, Uterotubal gas insufflation. *B*, Insufflation after excision of half of ampulla. *C*, Insufflation after excision of entire ampulla. *D*, Insufflation after excision of half of isthmus, showing an occasional shallow contraction. *E*, Insufflation after excision of entire isthmus. Note absence of manometric fluctuations.

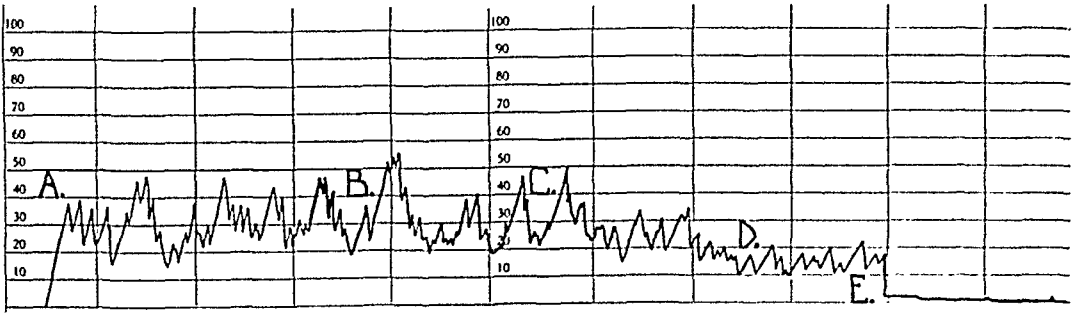


Fig. 3.—*A*, Tubouterine gas insufflation. *B*, Insufflation after excision of uterus. *C*, Insufflation after excision of tubouterine junction. *D*, Insufflation after excision of half of isthmus. *E*, Insufflation after excision of entire isthmus. Contractions have disappeared.

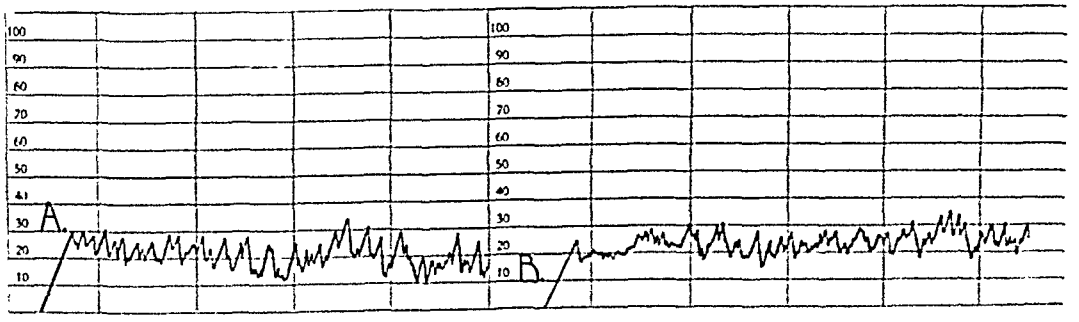


Fig. 4.—*A*, Uterotubal gas insufflation. *B*, Insufflation of tube (uterus excluded). Note similarity of manometric fluctuations recorded.

In 12 tests there were less than 4 contractions per minute; during uterotubal insufflation there were always more than 4 contractions per minute. In 14 experiments uterotubal insufflation registered 10 to 16 contractions per minute; when the uterus alone was insufflated there were never more than 9 contractions per minute. The uterine contractions usually had a larger amplitude than those which were obtained at uterotubal insufflation. When the uterus alone was insufflated, there were

only 9 tests with contractions of an amplitude less than 15 mm. Hg, the others having a range of 15 to 50 mm. Hg. During uterotubal insufflation there were 24 tests in which the contractions had an amplitude less than 15 mm. Hg, and only 6 with a depth of 15 to 30 mm. Hg.

EFFECT OF EXCISING SEGMENTS OF TUBE AND UTERUS, AND UTEROTUBAL JUNCTION

During nine uterotubal insufflations successive segments of tube from the fimbria toward the uterus were excised, eventually cutting off the uterotubal junction. Usually, a momentary rise in pressure resulted from the excision. However, after a minute or less the contractions regained their usual pattern.

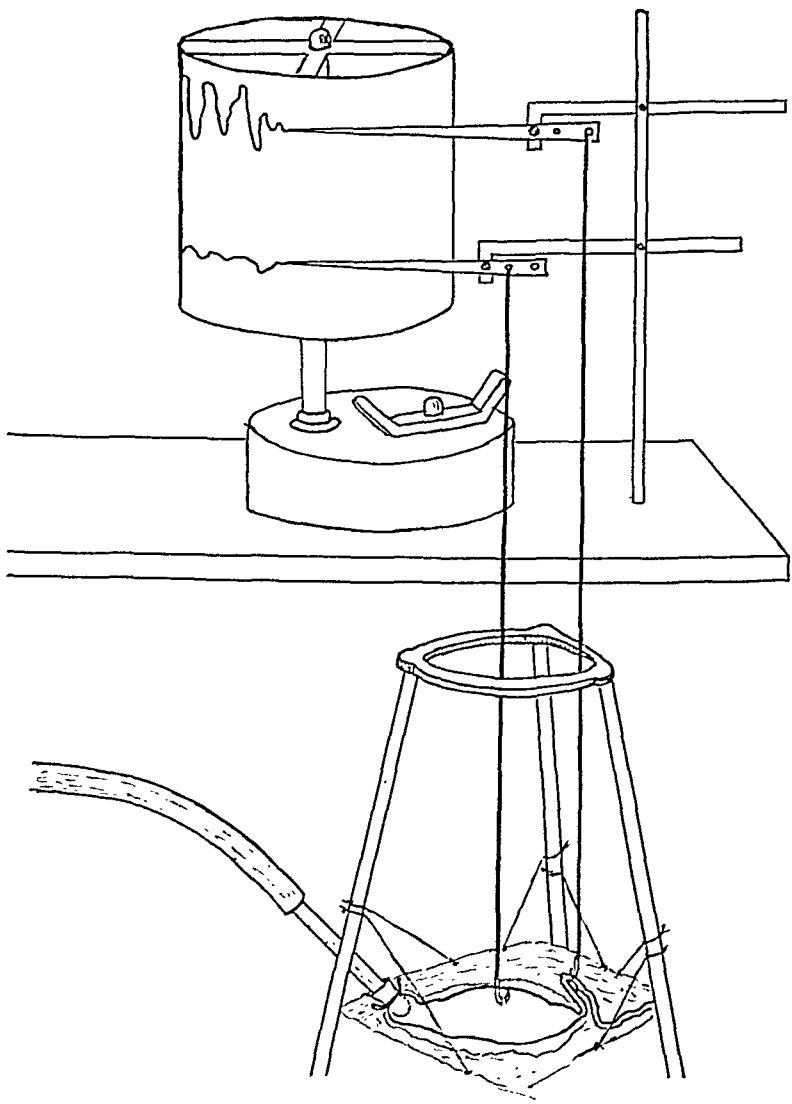


Fig. 5.—Sketch showing uterine and tubal muscle lever preparation with cannula for gas insufflation leading to the Rubin apparatus.

Excision of the outer third of the tube did not affect the character of the contractions. Excision of the entire ampulla, leaving the isthmus, did not affect the depth of contractions, but in one-third of the tests the contractions were slightly less frequent and were maintained at a lower pressure level. When only half of the isthmus remained, the contractions were rare and at a much lower pressure level.

As long as any portion of the tube remained, manometric fluctuations were recorded on the kymograph.

In four tests in which gas had passed the uterotubal junction at pressures below 50 mm. Hg, the uterus was not distended and muscle tone was retained. The result was an occasional weak manometric fluctuation from the uterus when the entire tube and uterotubal junction were excised. In five tests which required high pressures so that the uterus was markedly distended during uterotubal insufflation, no contractions occurred when the tube and uterotubal junction were excised (Fig. 2).

In ten experiments tubouterine insufflation was performed through a needle cannula, tied in the fimbriated end of the tube. When the entire uterus was excised up to the uterotubal junction, no change was noted in the manometric fluctuations. Excision of the uterotubal junction merely resulted in a slight lowering of the base line at which the manometric changes occurred. Excision of half of the isthmus

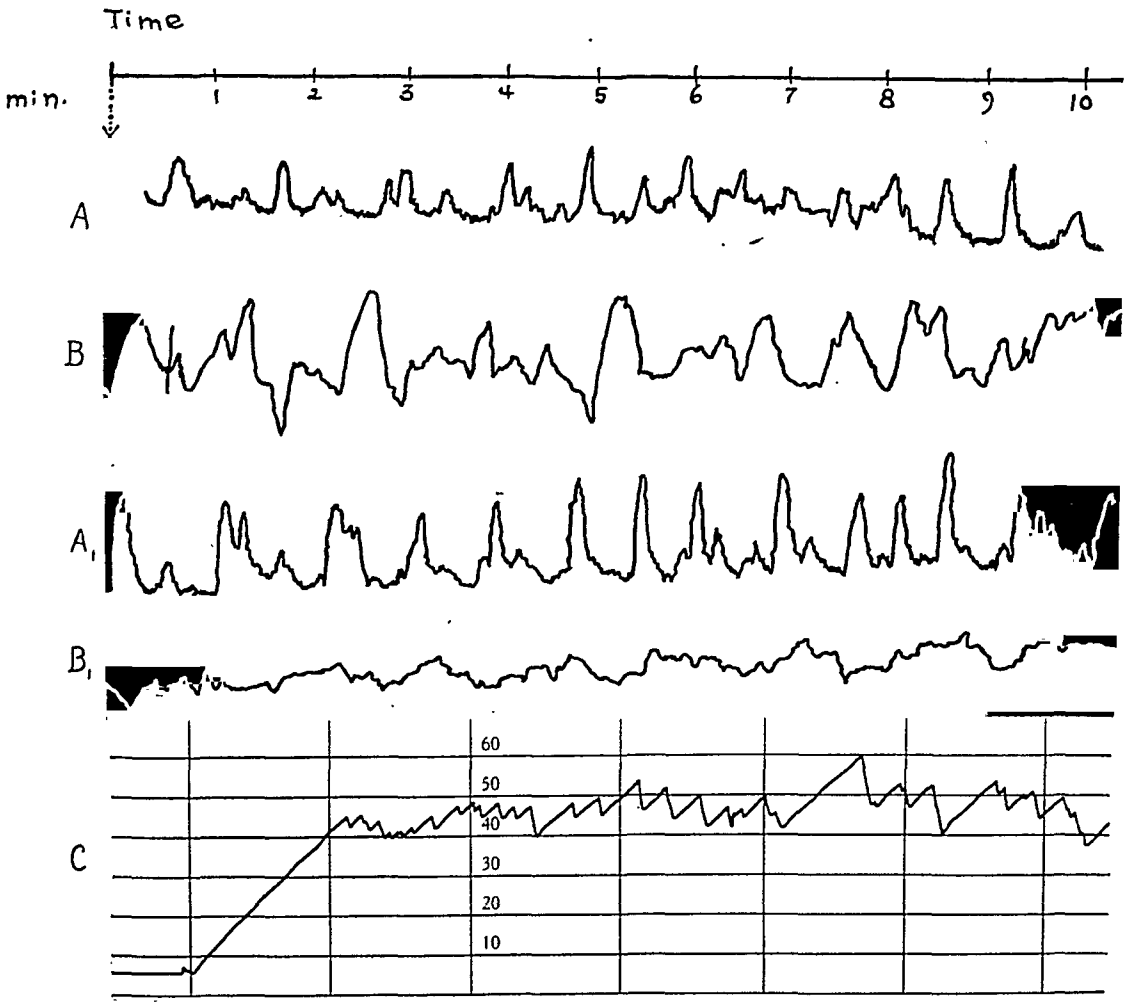


Fig. 6.—*A*, Contractions registered by hook in tubal muscle. *B*, Contractions registered by hook in uterine muscle. A_1, Contractions registered by hook in tubal muscle during uterotubal insufflation, showing no alteration in strength. B_1, Contractions registered by hook in uterine muscle during uterotubal insufflation, showing diminished muscle action. *C*, Contractions registered by uterotubal gas insufflation on the kymograph of the Rubin apparatus during the recording of A_1 and B_1.

did not affect the depth of contractions. In three tests, there were 2 to 3 contractions more per minute. There was a drop of 10 to 30 mm. Hg in the pressure level at which the gas maintained itself. When all of the isthmus was excised, gas bubbled through the ampulla almost continuously at a level of 0 to 8 mm. Hg, with the production of an occasional weak manometric fluctuation (Fig. 3).

From the above experiments, it appears that the uterus exhibits contractions during uterotubal insufflation only when it is not distended.

Excision of successive segments of the Fallopian tube indicates that the ampulla has very little power of contractility, and that this property is relegated to the more muscular isthmus.

COMPARISON OF UTEROTUBAL AND TUBAL INSUFFLATION

In six experiments, an opportunity was afforded to compare the pressure changes recorded by uterotubal insufflation with those obtained by insufflating the tube alone. Following uterotubal insufflation, a needle cannula was passed through the uterotubal junction and pressure changes were recorded during insufflation of the tube itself.

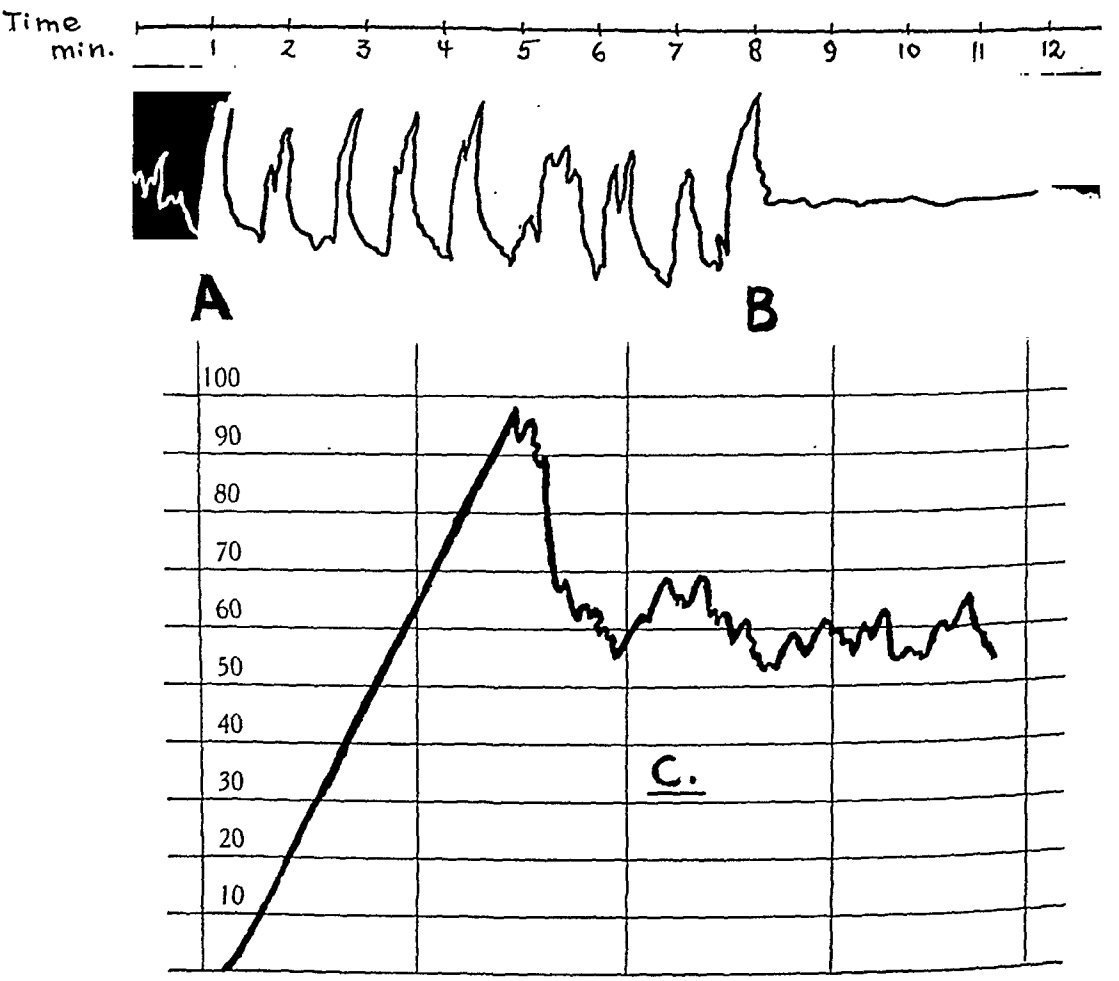


Fig. 7.—*A*, Contractions registered by hook in uterine muscle. *B*, Uterotubal gas insufflation was performed, resulting in an absence of uterine muscle function. *C*, Manometric fluctuations recorded on the kymograph of the Rubin apparatus, corresponding to the recording of *B*.

The manometric fluctuations obtained during uterotubal and tubal insufflation were similar. There was no noticeable difference in the contraction rate. During uterotubal insufflation the contractions were occasionally deeper, and higher pressures were required to force gas through the narrower uterotubal junction (Fig. 4).

CONTRACTION STRENGTH OF UTERINE AND TUBAL MUSCLE DURING UTEROTUBAL INSUFFLATION

The contraction strength of uterine and tubal muscle during uterotubal insufflation was determined in five rabbits in vivo by placing a hook in the uterine

muscle and another in the tubal muscle, and registering muscle action of both simultaneously on a smoked drum. Before insufflation, strong contractions of both the uterine and tubal muscle were seen. During uterotubal insufflation, the tubal muscle action was unaltered. The uterine muscle contractions nearly disappeared in 3 experiments and were absent in 2 others (Figs. 5 and 6).

In five other experiments, a solitary needle hook was placed through the uterine muscle and recordings made on a smoked drum before and during uterotubal insufflation. Before insufflation, large uterine contractions were observed. During insufflation, a rare contraction occurred in three instances and none were noted in two experiments (Fig. 7).

To eliminate the effect of extraneous factors such as intestinal and respiratory movements, these experiments were repeated on the excised uterus and tubes of seven rabbits, suspended in oxygenated Locke solution. No effect was noted on tubal muscle function during uterotubal insufflation. In the undisturbed state strong uterine muscle contractions were recorded on the smoked drum. However, when the uterus became distended by the insufflated gas, muscle contractions were rare or entirely absent.

In the above experiments, the hook on the uterus did not cause any change in the manometric fluctuations recorded on the kymograph of the Rubin apparatus during uterotubal insufflation. Only when the hook in the tubal muscle prevented free movement of the tube, did the manometric fluctuation become weaker, irregular, or absent. Similar results were observed when the uterus and tube were alternately fixed to the abdominal wall by sutures.

From the above observations, it appears that distention of the uterus as produced by uterotubal insufflation, results in a diminished or absent function of the uterine muscle. The tube, on the other hand, shows no visible distention and its muscle function remains unaltered. The diminished or absent muscle action of the uterus, when insufflated, would limit its participation in the production of manometric fluctuations during uterotubal gas insufflation.

SUMMARY

Experimental observations were made on the uteri and tubes of 60 living rabbits to determine whether or not the uterus participates in the production of manometric fluctuations, which are uniformly seen during uterotubal gas insufflation.

Manometric fluctuations occurred during uterotubal insufflation only when tubal patency was present.

The undisturbed uterus and tubes were seen to undergo rhythmic peristaltic movements. During uterotubal insufflation the uterus became distended and its motion was reduced or disappeared. The tube, on the other hand, showed no visible distention and its motion was unaltered.

The character of the contractions obtained by insufflating a solitary uterus was entirely different from the pattern recorded during uterotubal insufflation.

Excision of successive segments of the tube during uterotubal or tubouterine insufflation showed that the ampulla has very little power of contractility, and that this property is possessed by the more muscular isthmus. During tubouterine insufflation, excision of the uterus had no effect on the production of manometric fluctuations.

When the tube alone was insufflated, there was no noticeable difference in the character of the contractions obtained with the uterus

excluded, showing definitely that the latter did not have any influence in the production of the contraction waves as demonstrated on the kymograph of the Rubin apparatus.

Recording uterine and tubal muscle function during uterotubal insufflation by means of delicate hooks in the muscle attached to writing levers on a smoked drum, revealed that distention of the uterus resulted in a diminished or complete absence of function. The patent tube, on the other hand, does not become overdistended by any pressure levels during gas insufflation, and its muscle function remains unimpaired.

CONCLUSION

Experiments on rabbits indicate the limited degree to which the kymographic curves of pressure fluctuations (rhythmic contractions) observable during uterotubal insufflation are influenced by the uterine muscle, and that therefore these manometric fluctuations are due to the unimpeded action of tubal muscle in freely patent tubes.

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PREGNANCY WITH LEUCEMIA*

A Case Report and Review of the Literature

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A YEAR ago the authors saw a woman with acute lymphatic leucemia, which became apparent in the fifth month of her second pregnancy. This case is herewith reported:

Mrs. C. B. D., aged 29 years, was cared for by one of us in 1935 through her first pregnancy which was uneventful. The Wassermann was negative and blood findings were normal. The baby is alive and well.

Her past history was entirely normal except for the usual childhood diseases. Her tonsils had been removed. Menstruation had always been normal. A chronic ear infection had persisted for years.

She came under observation for this pregnancy on March 20, 1937. Her last menstrual period was Dec. 5, 1936. No abnormal findings were noted. The hemoglobin was 81 per cent and the erythrocytes 4,120,000. There were no unusual complaints until May 12, 1937, when she developed headache, malaise, frequent stools, and a low grade fever. These symptoms disappeared in a few days on rest in bed, a liquid diet, and a few doses of paregoric. However, on May 22, they returned and she noticed in addition, petechiae on the arms and legs, enlargement of the cervical glands and bleeding from the gums. A blood examination was made at this time which revealed: hemoglobin 48 per cent, erythrocytes 2,250,000, leucocytes 295,000 with 97 per cent lymphoblasts. The platelet count was 93,000. Hospitalization was advised but refused. She remained in bed until entering the hospital on May 30.

*Presented at the meeting of the Chicago Gynecological Society, May 20, 1938.

A physical examination on admission showed in addition to the above findings: no petechiae in the eyes or mouth; a normal tongue and marked adenopathy of the occipital and axillary nodes. Only the cervical nodes were tender. There was no enlargement of the heart but a slight systolic murmur was heard at the apex. The lungs were clear. There were numerous areas of hemorrhage under the skin from previous minor bruises of the extremities. The liver and spleen were palpable two fingerbreadths below the costal margins. The fundus of the uterus was at the level of the umbilicus. A blood smear showed almost exclusively lymphoblasts. The coagulation and bleeding times were abnormally long.

A diagnosis of acute lymphatic leucemia was made. Interruption of the pregnancy was considered inadvisable at this time because of the danger of hemorrhage and the child was not viable. Blood transfusions were given four times in the next eight days because of the anemia. There was some improvement in the hemoglobin and the number of red cells but very little reduction in the lymphoblasts. The patient felt a little subjective improvement. The size of the liver and spleen was slightly reduced. The patient wanted to go home. X-ray therapy was decided upon and 50 r. were given over the entire body excluding the uterus. She went home the same day, June 9, 1937.

Three days later she returned with severe pain in the left hypochondrium. The abdomen was distended with flatus and by the greater enlargement of the liver, spleen, and uterus. An enema gave some relief. There was marked bleeding from the nose and swollen lips and gums. The nodes previously mentioned were much larger and the inguinal nodes were now tender and palpable. The next day she complained of red spots before her eyes.

All these symptoms and findings increased in severity. On June 17 blood appeared in the urine and occult blood was found in the stools. Because of a decrease in the hemoglobin and erythrocytes another transfusion of 500 c.c. of citrated blood was given. After the x-ray therapy there was a decided reduction in the number of lymphoblasts. By the twenty-second of June there was another rise and so she was given a second treatment with x-ray. Again a reduction was noticed in the lymphoblasts, but the patient's condition appeared to be worse.

The next day about 4:00 P.M. painful uterine contractions began. After receiving one international unit of proluton these subsided until 9:00 P.M. when labor was again definitely in progress. She had been irrational for several hours. Her temperature was 102° F. By 10:00 P.M. the cervix was dilated to 4 cm. Morphine gave some relief from pain. At 11:30 P.M. 20 c.c. of thromboplastin was given intravenously because of fear of hemorrhage with delivery. At 2:30 A.M. on the twenty-third of June the dilatation of the cervix was 5 to 6 cm. and the membranes were ruptured artificially. At 3:15 A.M. a living male fetus was delivered spontaneously in frank breech presentation after six and a quarter hours of labor. There was moderate bleeding during labor. The placenta was easily expressed. The uterus contracted well, but moderate bleeding continued. It was packed with eight yards of gauze. About 400 c.c. of blood was lost. She was immediately given 300 c.c. of normal saline and 300 c.c. of citrated blood by transfusion. On leaving the delivery room, the patient's pulse was 140, and the blood pressure was 90/72. By 9:00 A.M. her pulse was 100 and the temperature 98.6° F. She felt better than she had for several days. At 10:15 A.M. 400 c.c. more of blood was given. By 4:00 P.M. her temperature was 104.4° F., pulse 120, and respirations 26. The uterus was no longer firm and bleeding through the pack began in spite of the use of ergotrate. At 6:30 P.M. the pack was removed followed by several large clots.

The patient was unconscious and in such extreme condition that it seemed useless to repack. At 7:30 P.M. 20 c.c. more of thromboplastin were given. By 11:30 P.M. copious involuntary bloody stools were repeatedly passed and uterine hemorrhage continued. The patient died at 6:05 A.M. on June 24, twenty-seven hours after delivery and forty-three days after the appearance of her first subjective symptoms of leucemia. This was thirty-three days after the diagnosis was confirmed by complete blood examination. The baby lived for six hours. It weighed 1,280 gm. The autopsy showed no evidence of leucemia in the baby. A blood examination before death was as follows: hemoglobin 12.5 gm., 81.8 per cent; red blood cells 3,870,000,

TABLE I. TEMP.—HEMATOLOGY—THERAPY

1937	MAY 30	JUNE 1	JUNE 9	JUNE 12	JUNE 17	JUNE 22	JUNE 23
Temp.	100.2	100.4	98.4	99.8	100	102.2	105.8
Pulse	106	106	90	128	106	126	140
Hb. gm.	-	7.5	10.5	10	6	5.5	6
Hb. %	48	48.7	68.1	64.9	39	37.7	38.9
R.B.C. Millions	2.45	3.02	3.78	3.41	2.49	2.82	2.66
W.B.C. Thousands	295	410	265	124	48	75	48
Platelets		78,520			43,200	36,480	
Transfusions	4 times—500 c.c.				500 c.c.		700 c.c.
X-ray	50 r.					50 r.	

white blood cells 38,700. Differential; polymorphonuclears 25 per cent, lymphocytes 45 per cent, mononuclears 5 per cent, eosin 5 per cent, myelocytes 10 per cent, lymphoblasts 10 per cent. This was not considered abnormal for a newborn infant.

*Necropsy Report.**—Only the essential pathologic findings are reported. The histopathologic picture had been altered by the agonal invasion of *Clostridium welchii.* This terminal infection had caused areas of extensive necrosis with gas formation.

The body was that of a 29-year-old, fairly well-nourished, pale, white female. Cutaneous petechiae were distributed over the body. The lymph nodes of the anterior cervical triangles, the axillae, and inguinal regions were enlarged, discrete, and moderately firm.

Leucoblastic infiltrations were present in the form of discrete and confluent, pinhead-sized nodules throughout the myocardium, lungs, hyperplastic mammary glands, liver, kidneys, uterus, ovaries, uterine tubes, gastrointestinal tract, pancreas, and suprarenal glands. There was considerable pulmonary edema present. *Clostridium welchii* were isolated from the heart blood and spleen.

It is not within the scope of this paper to discuss the histogenesis of blood cells or the etiology of the leucemias. Although cognizant of the debatable question of identification of the type cell present in any given case of acute leucemia, we are inclined to believe this patient suffered from the lymphatic form of the disease. This assumption is based upon (1) daily study of the blood smears stained with Wright's stain, Giemsa's stain and Goodpasture's peroxidase reaction. (2) Absence of Auer's bodies. (3) The distribution of the leucoblastic cells as well as their cytoarchitecture. The marrow of the sternum, ribs and femur was firm and pale gray red.

Microscopic Description.—Bone marrow (femur): Few fat cells were present. There was marked hyperplasia of the undifferentiated cellular syncytium with beginning basophilia of the cytoplasm of the reticulum cells. The chromatin structure had become more condensed. There were many free transitional forms in the veins and sinuses characterized by mononuclear, nongranular basophilic cells. The two cell types which are present in the greatest numbers are:

1. A large cell with a narrow rim of basophilic protoplasm surrounding a large nucleus. The nucleus was either irregular, round, slightly indented, or kidney-bean in shape, and occupied a slightly eccentric position with the excavation directed toward the larger accumulation of protoplasm. The nuclear membrane was coarsely outlined. In the nuclei there were various sized chromatin particles scattered widely apart in a large quantity of clear nucleoplasm. One or several nuclei were seen. Single nucleoli were situated near the nuclear indentation.

2. A smaller and more basophilic mononuclear nongranular cell with a hyperchromatic, coarse, granular, or slightly leptochromatic nucleus with a distinct nuclear membrane containing nucleoli and surrounded by a slight pink-blue narrow rim of cytoplasm. Many of these cells were in mitoses. These two types of im-

*Autopsies were done on mother and babe by Dr. E. L. Benjamin, the pathologist of the Evanston Hospital.

mature lymphocytes were present in far greater numbers than were other cytologic elements. They were distending the small veins, the sinuses and extrasinusoidal reticulum. Rarely was a promyelocyte or myelocyte present. Relatively few erythrogonia and erythrocytes were present. An occasional histiocyte containing waste pigment and pyknotic nuclear material was seen. Pyknotic fragmented nuclear material was seen lying free in the reticulum fibers.

Irregular focal areas of degeneration and necrosis were present throughout the bone marrow. The centers of such areas contained many large bacilli with flat ends *(Cl. welchii)*.

Lymph Nodes.—The cervical, axillary, inguinal, tracheobronchial, hepatic and to a lesser extent the periaortic and mesenteric lymph nodes were most noticeably involved. They ranged from 1.5 cm. to 2.5 cm. in diameter. The tracheobronchial lymph nodes were anthracotic. The others were pale gray. All were soft and enveloped by an intact capsule.

Microscopic Description.—All of the nodes examined displayed a diffuse reticulum cell hyperplasia with formation of immature lymphocytes. The primary and secondary follicles were indistinguishable. The trabeculae and capsule were heavily infiltrated with the type cell. The subcortical sinuses were filled with lymphocytes, histiocytes, and macrophages. The tremendous crowding of the leucemia infiltration rendered reticulum almost indistinguishable in some areas of the cortex and medulla. Mitoses of the lymphocytes were numerous. The small intrapulmonic lymph nodes still retained a trace of their normal architecture.

Spleen.—Weight 952 gm. The capsule was smooth. Surfaces made by sectioning, everted. The uniform red pultaceous substance was crepitant and somewhat spongy. The extensive degeneration by the agonal invasion of *Cl. welchii* rendered the sections unfit for microscopic study.

Reference to standard textbooks on obstetrics gave very little information as to prognosis and management. A desire for further knowledge prompted this review of the literature. It was found that the last review in this country was made in 1925 by Bower and Clark, who collected 17 cases. Kosmak, in 1921, had described 12. Since then more complete collections have been made in Europe by Neumann and Hofstein. The latest and most inclusive review was made in Italy by Garrassi in 1934 who found 59 cases. Not all of these were sufficiently clear for study. He gave credit to Debiasi for most of his collection and added several more. The authors have been able to find 74 cases, including those mentioned by the above authors, at least 8 of which have been published since Garrassi's study. To this series our own case is added, which brings the total to 75. Thirteen of this number had only bibliographic mention or were not reported in sufficient detail. Nine others were well enough described to include but were not classified. Thus we have 62 cases on which to base this study.

It was found that all cases were divided into two main groups, namely, acute and chronic. All of the chronic cases were myelogenous. Russell reported a case of chronic lymphatic leucemia, but because of the short duration of the disease and the early death of the patient we have included it in the acute group. Certainly it could be called subacute. There were 8 cases in the acute group which were called acute lymphogenous, including our own. Eleven were myelogenous. Two were diagnosed as acute hemocytoblastic and two others were not differentiated.

ONSET IN RELATION TO GESTATION

In the 25 acute cases it was believed the onset most often occurred during gestation. Only 5 started before pregnancy and but one of these as long as three months.

Eighteen cases started after conception, 7 in the first half and 10 in the last half of pregnancy. The month was not stated in one. The average time of onset was the fifth month. The time of onset was not mentioned in two others.

The onset in the 28 chronic cases was most often prior to conception. In 15 this varied from one to five years; in 3 from six months to a year and less than six months in one. In 3 cases it was not stated how long before. Five women had their first symptoms during pregnancy, 3 in the first half and one in the last half of gestation. In one the month was not stated. In one other no mention of the time of onset was made. When the onset was during pregnancy the average was in the fourth month.

TABLE II. ONSET OF LEUCEMIA IN RELATION TO GESTATION

	CHRONIC CASES	ACUTE CASES
Prior to Gestation		
1 yr. to 5 yr.	15	0
6 mo. to 1 yr.	3	0
Less than 6 mo.	1	4
Not stated	3	1
During Gestation		
First 4½ mo.	3	7
Last 4½ mo.	1	10
Not stated	1	1
Unknown	1	2

TABLE III. WHEN DELIVERED

PERIOD OF GESTATION	CHRONIC CASES	ACUTE CASES
Term	14	5
Premature 7 to 8½ mo.	6	10
Immature 4½ to 7 mo.	4	6
Abortion 4½ mo. or less	3	0
Undelivered—died	1	4

WHEN DELIVERED

In the acute cases four women died before delivery. Five went to term, 10 delivered prematurely (seven to eight and one-half months), 6 immaturely (four and one-half to seven months), and none aborted.

Of the chronic cases 1 woman died before delivery. Fourteen went to term, 6 delivered prematurely, 4 immaturely, and 3 aborted.

HOW DELIVERED

In the acute cases 15 delivered spontaneously. Six had operative deliveries, including 2 cesarean sections, 2 forceps deliveries and 1 version and extraction.

Among the chronic cases there were 22 spontaneous births, 3 induced abortions and 2 operative deliveries, including a cesarean at eight months and a hysterotomy at five months. Three of the spontaneous labors were induced.

HEMORRHAGE

In the acute cases hemorrhage was reported only five times. In but one case was it said to have been fatal. In another case bleeding occurred from the clitoris which was controlled with difficulty.

TABLE IV. HOW DELIVERED

	CHRONIC CASES	ACUTE CASES
Spontaneous term	22	15
Induced abortions	3	0
Operative	2	6
Undelivered	1	4

TABLE V. HEMORRHAGE

	NOT FATAL	FATAL
Chronic cases	7	0
Acute cases	4	1

In the chronic cases there was no fatality from hemorrhage during delivery. It was only reported seven times. Most authors commented on the lack of bleeding in delivery in both groups.

MATERNAL RESULTS

Only two women lived as long as five weeks after delivery in the acute cases, 14 died within fifteen days, 5 died in labor, and 4 died undelivered, a maternal mortality rate of 100 per cent.

The result for the mothers was strikingly different in the chronic cases. Twenty-three were alive two and one-half months after delivery, though 5 of these were dead within eight months. Four died in the puerperium and 1 died undelivered, a maternal mortality rate of 17.8 per cent.

In the 9 unclassified cases two women lived more than two and one-half months, 2 died within fifteen days of delivery, and another in five weeks. One was still alive and pregnant when the case was reported. The fate of 3 was not stated. Thus in the 58 patients delivered where the fate of the mother was stated, the mortality was 51.7 per cent, including deaths within two and one-half months after delivery.

FETAL RESULTS

No woman in the acute group had more than one pregnancy and there were no multiple births. Eight babies lived, 17 died, a fetal mortality rate of 68 per cent. Four of these died in utero and 13 were stillborn or were neonatal deaths. The principal cause of death was prematurity.

In the 28 chronic cases there were 33 pregnancies and 35 babies; 21 lived, 12 died or were stillborn, 5 viable and 7 not viable. One died in utero and in another the result was not stated. The fetal mortality rate was 37.1 per cent. The fate of the babies was remarkably good when delivered after the seventh month. None of the babies in either group had leucemia.

TABLE VI. MATERNAL RESULTS

	CHRONIC CASES	ACUTE CASES	UNCLASSIFIED CASES
Lived 2½ plus mo.	23	0	2
Died undelivered	1	4	0
Died in labor	0	5	0
Died within 15 days	4	14	2
Died within 5 weeks	0	2	1
Fate not given	0	0	3
Still alive and pregnant	0	0	1

TABLE VII. FETAL RESULTS

	CHRONIC CASES	ACUTE CASES	UNCLASSIFIED CASES
Pregnancies	33	25	9
Children	35	25	9
Lived	21	8	5
Died, 7 plus mo.	5	7	0
Died, under 7 mo.	7	6	2
Died, in utero when mother died undelivered	1	4	0
Fate not given	1	0	1
Mother still alive not delivered	0	0	1

TABLE VIII. ACUTE LEUCEMIAS

CASE	AUTHOR	YEAR	AGE	PARA	RELATION OF ONSET TO GEST.	PERIOD GESTATION DELIVERY		HEMORR.	RESULTS	
						WHEN	HOW		MOTHER	CHILD
1	Kerstein-Hilbert	1893	37	v	7th mo.	Term	Spont.	None	Died 3rd stage	Stillborn
2	Merttens	1900	30	i	4½ mo.	Undeliv.	-	-	Died with first pains	
3	Lazarus and Fleischmann	1905	40	xii	4th mo.	5 mo.	Spont.	Fatal 3rd stage	Died 3rd stage	Stillborn Nonviable
4	Bostetter	1906	23	i	7th mo.	Undeliv.	-	-	Died 7th month	Undelivered
5	Thaler	1914	40	ix	6th mo.	Term.	Spont.	None	Left hospital ill; probably died	Stillborn
6	Petersen	1914	24	i	6th mo.	8 mo.	Spont.	None	Died few hr. P.P.	Lived
7	Lindbrones	1920	25	iii	2nd mo.	Undeliv.	-	-	Died undelivered	
8	Kosmak	1921	25	iii	3rd mo.	Undeliv.	-	-	Died undelivered	
9	Kosmak	1921	35	iv	?	5 mo.	Ind. spont	None	Died 15th P.P. day	Lived?
10	Fleischmann	1923	30	iii	Prior	8 mo.	Cesarean	None	Died 11th P.P. day	Stillborn
11	Frank	1924	32	i	7th mo.	Term	High forc.	None	Died 6th P.P. day	Lived?
12	Allen	1928	20	i	3rd mo.	7 mo.	Vers. & ext.	Yes	Died 5th P.P. day	Stillborn
13	Saidl (2nd)	1931	25	?	1 mo. prior	8 mo.	Spont.	None	Died P.P. Atony	Died
14	Mann	1931	23	iv	2 mo. prior	7 mo.	Spont.	None	Died 5th P.P. day	Lived
15	Debiasi (2nd)	1931	15	i	7th mo.	8 mo.	Spont.	Yes	Died 11th P.P. day	Lived 56 d.
16	Held	1931	38	iv	?	Term	Extract.	None	Died 3rd stage	Stillborn
17	Heim	1932	26	?	3rd mo.	Term	Spont.	None	Died 8th P.P. day	Lived
18	Russell	1933	22	iii	3rd mo. prior	8½ mo.	Spont.	3rd stage	Died 5 wk. P.P.	Lived
19	Hüssy	1934	35	iii	During preg.	7½ mo.	Cesarean	None	Died 24 hr. P.P.	Lived
20	Traina	1937	28	i	3 mo. prior	5 mo.	Spont.	None	Died 2nd P.P. day	Stillborn
21	Zanela	1937	25	ii	4th mo.	6 mo.	Spont.	None	Died 3rd stage	Stillborn
22	Zanela	1937	22	i	5th mo.	6 mo.	Spont.	None	Died 8th P.P. day	Stillborn
23	Mehta	1937	18	i	7th mo.	7¼ mo.	Low forc.	None	Died 2nd stage	Stillborn
24	Grier	1938	29	ii	4½ mo.	6½ mo.	Spont.	None	Died 27 hr. P.P.	Died in 12 d.
25	Wallgren	?	29	i	7th mo.	7½ mo.	Spont.	410 c.c.	Died 11th P.P. day	Stillborn

TABLE IX. CHRONIC LEUCEMIAS

CASE	AUTHOR	YEAR	AGE	PARA	RELATION OF ONSET TO GESTATION	PERIOD GESTATION DELIVERY		HEMORR.	RESULTS	
						WHEN	HOW		MOTHER	CHILD
1	Cameron	1888	36	vii	2 yr. prior	7 mo.	Spont.	None	Lived	Lived
2	Sänger	1888	32	iii	Prior concep.	7 mo.	Ind. Spont.	None	Lived	Lived
3	Laubenberg	1891	32	vii	Prior concep.	5 mo.	Spont.	None	Died—40 hr.	Nonviable
4	Schroder	1898	26	viii	Prior concep.	6 mo.	Ind. Spont.	None	Lived	Nonviable
5	Joachim	1906	39	?	7 mo. prior	Term	Spont.	None	Lived	Lived
6	Savarre	1909	27	iii	3rd month	Term	Spont.	None	Lived	Lived
7	Savarre	1909	30	v	6th month	Term	Spont.	None	Died—11th d.	Stillborn
8	Kleineberger	1913	39	?	2½ yr. prior	Term	Spont.	None	Lived	Lived
9	Melnikoff and Tsomakion	1913	?	?	?	Term	Spont.	None	Lived	Lived
10	Gasser	1914	38	iii	7½ mo. prior	5 mo.	Ind. Spont.	10th d.	Lived 8 mo.	Nonviable
11	Renon and Degrais	1920	?	i	1 yr. prior	Term	Spont.	None	Lived	Lived
12	Meurer	1921	?	ix	1 yr. prior	8 mo.	Spont.	None	Lived	Twins—lived
13	Hausam	1922	28	ii	4 yr. prior	8½ mo.	Spont.	From clitoris	Lived 4 mo.	Lived
14	Chiari and Dautwitz	1924	27	i	1 yr. prior	Term	Spont.	None	Lived	Lived
15	Thamer	1925	28	ii	5 yr. prior	8 mo.	Cesarean	None	Died 11th d.	Stillborn
16	Bower and Clark	1925	24	i	5 yr. prior	Term	Spont.	None	Died—few hr.	Lived
17	Bower and Clark	1925	25	?	3rd month	-	No deliv.	None	Died 7th mo.	-
18	Neumann	1928	32	v	4 yr. prior	3 mo.	Ind. abort.	Yes	Lived 3¼ mo.	Nonviable
19	Ridder	1930	34	Mult.	3 yr. prior	Term	Spont.	None	Lived 2½ mo.	Lived
20	Neumann	1930	?	ii	2 mo. prior	3 mo.	Ind. abort.	Yes	Lived	Nonviable
21	Saidl	1931	35	iii	2 yr. prior	5 mo.	Hysterotomy	Yes	Lived	Nonviable
22	Webber	1931	38	iii	2 yr. prior	Term	Spont.	None	Lived 5 mo.	Twins—lived
23	Recek	1931	25	i	2 yr. prior	7 mo.	Spont.	10th d.	Lived	Died
24	Hofstein	1932	28	iv	2 yr. prior	2 mo.	Ind. abort.	None	Lived	Nonviable
25	Kaplan et al.	1932	26	ii	2½ yr. prior	Term	Spont.	None	Lived	Lived
26	Neumann	1932	35	iv	In 2nd mo.	Term	Spont.	None	Lived	Lived
27	Rydzewska	1932	37	Mult.	During preg.	Term	Spont.	Yes	Lived	Lived
28	Garrassi	1934	27	ii	7 mo. prior	Term	Spont.	None	Lived	Lived

TABLE X. INCOMPLETE DATA—NOT CLASSIFIED

CASE	AUTHOR	YEAR	AGE	PARA	RELATION OF ONSET TO GESTATION	PERIOD GESTATION DELIVERY		HEMORR.	RESULTS	
						WHEN	HOW		MOTHER	CHILD
1	Paterson	1870	?	i	5th month	Term	Spont.	Yes	Lived 10 days	Lived
2	Paterson	1870	?	i	5th month	Term	Spont.	Yes	Lived 14 days	Lived
3	Paterson	1870	?	iv	5th month	Term ?	Spont.	?	?	Lived
4	Ingle	1880	33	?	?	?	Spont.	?	?	Lived
5	Stillman	1890	34	vi	?	?	?	?	Lived 1 mo.	?
6	Suteliffe	1914	21	i	?	Ectopic 3 weeks	Laparot.	Yes	Lived	-
7	Renon and Degrais	1920	?	?	?	5½ mo.	Spont.	?	?	Nonviable
8	Jimenez G. de la Serrana	1921	40	vii	3 yr. prior				Still pregnant when reported	-
9	Debiasi	1931	27	iii	?	Term	Spont.	None	Lived	Lived

Cases With Bibliographic Mention Only or Not Leucemic

1. Greene	1888	6. Ohlson	1925	10. Lammers	1929
2. Jaggard	1890	7. Kaplan	1927	11. Labhardt	1932
3. Herman	1900	8. Bruggeman	1928	12. Pontoni	1937
4. Schenk	1922	9. Geller	1928	13. Donati	1937
5. Nagy	1924				

The course of the disease in the acute cases was quite short, comparable with the duration frequently quoted when pregnancy was not a factor. When the disease started during gestation the average life expectancy was about ten weeks. And since the average month of onset was the fifth, death usually occurred before term could be reached, the average being 7.3 months.

The course of the disease in the chronic cases was about the same as that commonly stated when pregnancy was not involved. Most of the women had the disease for two years and nine months before conception. As the average time when delivered was 7.4 months, thus the average duration of the disease was three years, 4.4 months. As 18 women were still alive when their cases were reported they probably lived longer than four years with leucemia in spite of one or more pregnancies. Of the 4 women who died in the puerperium 2 had leucemia for nearly six years when delivered, which is certainly near the end of life expectancy for any chronic case. Thus we can say that the course is not terminated fatally by pregnancy unless in the late years of the chronic disease. There is usually, however, an exacerbation of symptoms with pregnancy and a remission after delivery.

TREATMENT OF LEUCEMIA

Many forms of therapy have been employed for the cure of leucemia, namely, arsenic, benzol, sulphur, iodine, x-ray, radium, thorium, ultraviolet rays, endocrines, splenectomy and grafting of the spleen. In acute cases nothing has been successful. Blood transfusions give a temporary increase in hemoglobin and red blood cells. In the chronic forms, arsenic, x-rays, and radium have been successful in producing temporary remissions in the early years of the disease. Blood transfusions are helpful as stated above and also decrease bleeding and coagulation times. After repeated x-ray treatment a resistance develops which voids beneficial effects. In the acute cases x-ray may be harmful. In our case the patient was made more uncomfortable even though a definite reduction in the lymphoblasts was accomplished.

SUMMARY OF CONDUCT

Any woman with leucemia should be advised against pregnancy. Some authors even advise sterilization. In this series of acute cases very few became pregnant with leucemia in progress, and in these the disease was not present for longer than three months prior to conception. The symptoms are so grave and the course so short that pregnancy is not likely after the disease has once begun.

In the chronic forms pregnancy should be avoided, because of the acute exacerbations which occur at the time. Occasionally death is sudden after delivery, especially when taking place in the later stages of the illness. Fortunately some of these women are sterile. Only one case of chronic lymphatic leucemia with pregnancy has been reported.

Some authors attribute this to the extensive infiltration of the ovaries and endometrium which interferes with ovulation and implantation of the ovum. This does not seem to be so in the chronic myelogenous type as five women have become pregnant more than once. Should a woman, knowing her condition, insist on becoming pregnant, she may be allowed to do so, provided that the disease has not been present too long and that she be observed closely. X-ray therapy may cause a remission and might produce good results.

Should a woman be pregnant when the disease is discovered, what course should be advised? In the chronic forms the pregnancy may be allowed to continue and x-ray therapy employed. If the disease is of

recent origin the immediate prognosis for mother and baby is good. If of several years' standing the prognosis is not as good but no interference should be attempted. Some authors disagree with this, as Hofstein, Saidl and Neumann, who advise interruption in early pregnancy. We agree with Garrassi who advises against it. A premature or nonviable baby is the result and the mother is not benefited.

In the acute forms no therapy produces even a remission of symptoms. Some authors state that x-ray therapy in these cases merely aggravates the condition. X-ray sickness adds to the patient's discomfort. Interruption of pregnancy only shortens the woman's life and results in premature babies. Blood transfusion aids the secondary anemia, obviates loss of blood and increases coagulation time. It is a palliative measure. If the disease is present in the last trimester, induction of labor or cesarean section is justifiable to save the baby when the mother is near death.

CONCLUSIONS

1. The frequency of chronic and acute forms in this series is nearly the same, being 28 for the former and 25 for the latter; 9 cases were unclassified.

2. The course of the chronic cases may be as long as six years, during which time some women have been pregnant more than once. Exacerbation is the rule during pregnancy.

3. The course of the acute cases was remarkably short and all women died during pregnancy, labor or the puerperium.

4. Only one case of chronic lymphatic leucemia has been reported. All the other chronic cases were of the myelogenous type.

5. The majority of acute cases were myelogenous, the ratio with those of the lymphatic type being 11 to 8.

6. Premature labor is frequent in the acute cases, less frequent in the chronic cases.

7. The prognosis for the babies is good in the chronic cases after viability, less favorable in the acute cases because of the frequency of premature delivery.

8. None of the babies showed evidences of leucemia.

9. Hemorrhage during delivery of the baby and the placenta was conspicuously uncommon. No women died of uterine hemorrhage in the chronic cases and only one in the acute cases.

10. No treatment of leucemia has been satisfactory. In the chronic forms x-ray apparently aids in producing a temporary remission of the leucocytosis and the symptoms. Blood transfusion has a very transient effect on secondary anemia but is the only treatment of value in the acute leucemias.

11. Pregnancy should be avoided when leucemia is known to be present. Only in the chronic forms may it be permitted if the woman insists and if her condition is explained to her.

12. Interference with pregnancy does not help the mother in either form. It only tends to produce premature or nonviable babies. In the acute forms it shortens the mother's life.

13. Premature induction of labor or cesarean section is justifiable when near term to save the baby and when the mother is near death.

14. Age and parity had no influence in these cases.

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DISCUSSION

DR. HOWARD ALT.—I would like to praise part of the treatment and criticize another part. It appears that the transfusions did this patient a great deal of good, as on the third day her temperature began to come down, and on the fifth or sixth

day it was normal. The red cell count increased from two to four million. The white count after the last transfusion was 218,000, while the initial count was 410,000.

Just before discharge from the hospital she received an x-ray treatment. X-ray therapy is contraindicated in patients with acute leucemia, for if the dose is large, death may occur. On readmission to the hospital, the white count was low, but her condition was much worse. She again had a high fever and an increase in the purpura. A week or ten days later she received a second x-ray treatment, which was followed by the onset of labor within twenty-four hours. X-ray treatment has been used to induce labor, so it seems quite likely that the x-ray caused labor to begin in this case. It is possible that, if transfusions had been given once or twice a week and the x-ray omitted, the patient's life could have been prolonged sufficiently to obtain a viable infant. If acute leucemia occurs early in pregnancy, as Dr. Grier said, no interference should be attempted. If it occurs after the fifth month of pregnancy, it is frequently possible to obtain a live baby. In subacute leucemia the mother should be supported with blood transfusions until the fetus is viable.

I do not agree, however, with Dr. Grier on the management of pregnancy in chronic leucemia. It is reported that there is often an acceleration of the leucemia during pregnancy with improvement after the uterus is emptied. For this reason, it would seem best to determinate a pregnancy occurring early in chronic leucemia. The patient has enough of a load with the leucemia without adding the extra burden of pregnancy. If pregnancy occurs late in the course of chronic leucemia, the patient should of course be allowed to deliver spontaneously.

There are two main types of treatment in chronic myeloid leucemia: one is x-ray and the other arsenic. X-ray therapy should be withheld during pregnancy, as it cannot be given without danger to the fetus. Arsenic will produce a temporary remission in chronic myeloid leucemia, and at the same time will not hurt the fetus.

DR. HARRY A. RICHTER.—This patient's past history gives nothing of significance as an etiologic factor. There is a note of chronic otitis media and mastoiditis, following scarlet fever in childhood, but chronic infections have not been proved to be etiologic factors in leucemia.

Two years ago, three months after she had given birth to a normal boy, physical examination of this patient was negative and the blood picture normal. It would seem correct therefore that this case should be classed as "acute." The disease probably started during the course of the last pregnancy, or shortly before, the pregnancy causing an exacerbation of the disease.

The interruption of pregnancy during acute leucemia is attended by risk of hemorrhage and infection and often hastens the eventual fatality. It is generally considered that all forms of treatment in acute leucemia are of no avail, although blood transfusions tend to keep up the hemoglobin and red count and have less adverse effects than x-ray therapy, with its dramatic response in the reduction of white cells, glandular enlargements, and diminution in the size of the spleen and liver. Leucemic patients have little resistance to infection, and in acute leucemia, infection is usually present at the onset.

DR. C. D. HAUCH.—I wish to report a leucemia in a pregnant woman admitted to the Evangelical Hospital. She had had a severe leucemic crisis between her first and second pregnancies, but there were no definite symptoms of leucemia during the pregnancy. Therapeutic abortion was suggested but was advised against by the obstetric consultant. Pregnancy continued to term. Labor and the puerperium were normal. The baby is about one year old. The mother now has another leucemic crisis. No x-ray treatment was given or advised during pregnancy, but she has had two radiation treatments since.

DR. GRIER (closing).—The classification of leucemia is for the hematologist to decide, but from an obstetric viewpoint the division into acute and chronic is all that is necessary. Some of these so-called acute cases must have been really subacute.

The x-ray we used in this case may have done some harm. Her life expectancy at best was rather short with any therapy. The x-ray certainly did not aggravate her general condition and the leucocytosis was improved.

There have been only two men who have seen as many as three cases of leucemia with pregnancy, so I do not think any one man has had enough experience to take a decided stand. All of these conclusions I have drawn have been from the literature.

As to the interruption of pregnancy, I still believe it is not the thing to do. In cases where it was done the outcome for the patient was just as bad as when it was not done. In the early stages of the chronic group alone there may be some excuse for it. The cases allowed to go to term on the other hand did very well except where they had had the disease for five or six years.

GRANULOSA CELL TUMORS

With the Report of a 34 Pound Specimen and a Review

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ALTHOUGH granulosa cell neoplasm of the ovary had been described as early as 1855[8] the tumor did not receive the well-deserved attention it now commands until Robert Meyer's contribution in 1915. Since that time, however, Robinson, King, Novak, TeLinde, Schiller, Neumann and other investigators have made substantial additions to this gynecologic entity which, in view of the 300 cases reported, can no longer be considered as new. Consequently, in presenting our material, historic details will be summarily dismissed as these have been carefully considered in papers by Bland and Goldstein and others.

HISTOGENESIS

The concept of Robert Meyer, that these tumors arose from granulosa cell rests in the ovarian hilus is no longer tenable in its original form. Recent experiments by Butterworth have shown that granulosa cell tumors can be produced in mature female mice by the use of roentgen rays. The tumors, histologically and functionally entirely analogous to the granulosa cell tumors of women, appeared to spring directly from degenerating follicular epithelium.

CLINICAL FEATURES

Sixty per cent of granulosa cell tumors occur after the menopause, 30 per cent occur between puberty and the climacterium, and 5 to 10 per cent occur before adolescence. In childhood these tumors give rise to precocious menstruation with early sexual and somatic development. During the period of sexual maturity they produce either amenorrhea per se or amenorrhea followed by profuse and continuous menses. After the menopause, granulosa cell neoplasm gives rise to a periodic pseudomenstrual type of bleeding in 90 per cent of the cases.

The basis for these symptoms is to be found in the tremendous quantities of estrin elaborated by these tumors in all age groups. The hor-

mone can be demonstrated in the blood and urine of patients who have granulosa cell neoplasm and in almost unbelievable amounts in extracts of tumor tissue. Its action on the uterus is the production of myohyperplasia with a thick, boggy, proliferative type of endometrium often containing cysts. The exact mode by which a different syndrome is produced in the different age groups is not well understood.

PATHOLOGY

Ninety per cent of granulosa cell tumors are unilateral, 90 per cent are solid, and 90 per cent are of a relatively very low grade of malignancy. They vary in size from the pin head nodules described by TeLinde to large masses weighing 34 pounds (15.4 kg.) as in Case 1 described below. They appear to be well encapsulated. The cut surface has the homogeneous, granular appearance of liver sausage and this appearance allows one to make a correct gross diagnosis in 50 per cent of the cases. Microscopically the cylindroid, folliculoid and diffuse types of cellular pattern are so well known as to merit little description. They do not represent separate entities but may be found mixed even in the same microscopic slide.

MATERIAL

In a study of the solid and solid-cystic group of ovarian tumors removed surgically at The Mayo Clinic from 1905 to 1937, 30 examples of granulosa cell neoplasm were encountered. The specimens were all formalinized—a fact which precluded their study from the standpoint of hormone content. The clinical and pathologic data, however, are sufficiently clear to make possible an analytic study. The tumors were studied in gross, and interesting specimens were photographed. Multiple sections were then cut and stained routinely with hematoxylin and eosin. Lipoid stains were employed whenever indicated. Where possible, sections were made of the endometrium and of the unaffected ovary.

CASE 1.—A single, white nullipara, aged 37 years, was admitted to the clinic April 28, 1916, complaining of an abdominal tumor and amenorrhea. Her family and personal histories were negative. Menses had begun at the age of fourteen years and had been normal for ten years. For the succeeding twelve years she had had amenorrhea, except for an occasional episode of bleeding, moderate to profuse in amount. Eight years prior to admission she had first noticed a pelvic tumor which had steadily increased in size. Weakness, palpitation, and dyspnea had been present for six months.

Positive physical findings were the presence of marked emaciation and a huge pelviabdominal tumor. Positive laboratory data were a hemoglobin reading of 40 per cent and mild albuminuria.

At operation, May 5, 1916, a huge, solid, left ovarian tumor was removed. Adhesions or metastasis was not noted.

The postoperative course was uneventful and the patient returned home on the twelfth day. At a subsequent examination, in 1921, her menses were recorded as being normal. Neither at this time nor at a later visit, in 1935, was there any evidence of recurrence following this local operative procedure.

Grossly, the tumor weighed 34 pounds (15.5 kg.). It was firm, encapsulated, somewhat lobulated and grayish brown. On section, large, cystic regions of degeneration and hemorrhage were found. However, examination of the solid portions revealed granular homogeneity so characteristic that a diagnosis of granulosa cell neoplasm was made before the microscopic confirmation.

Microscopically, sections from various parts of the neoplasm all presented the same architectural pattern; namely the so-called cylindroid type of neoplasm, according to Meyer's classification (Figs. 1, 2, and 3).

CASE 2.—A married, white primipara, aged 31 years, presented herself for examination Feb. 8, 1921. Her family and personal histories had been entirely negative. Menses had begun at the age of fifteen years and had been normal until two and a half years prior to her registration, when flow had become scanty in amount and periods spaced further apart. Two years before the patient's admission, her menses had ceased entirely. For eight months a dull pain had been present in the left lower abdominal quadrant. For six months the patient had noticed bilateral mammary tenderness.

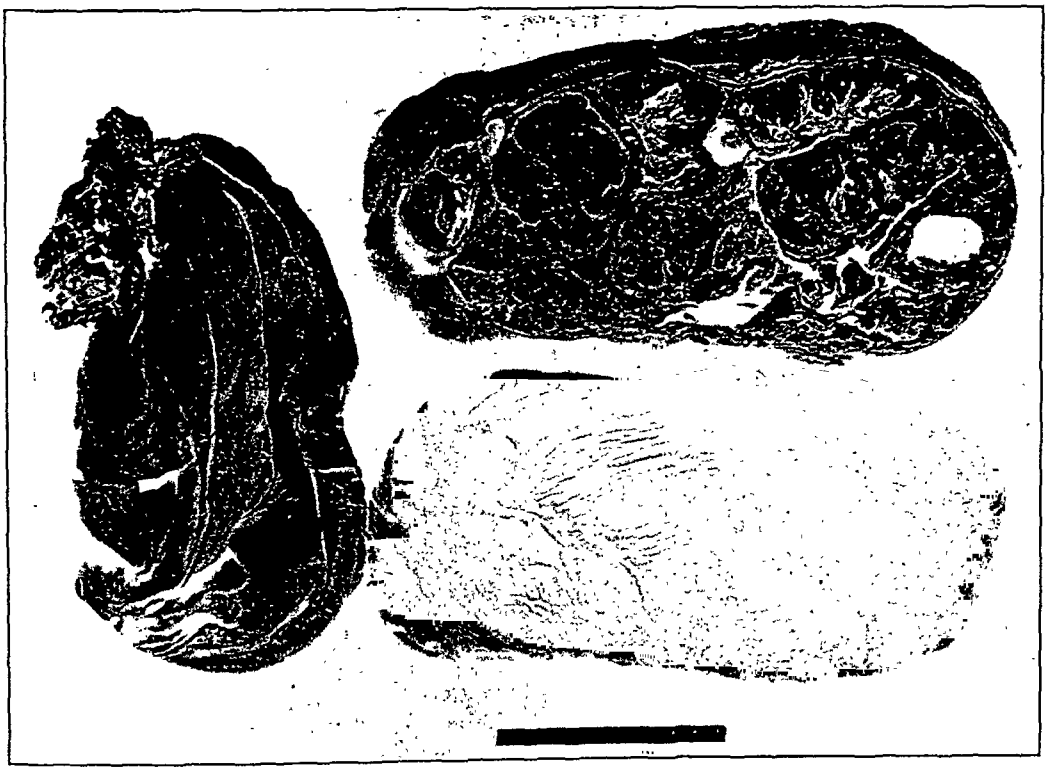


Fig. 1.—(Case 1.) Surface and sectional views of a granulosa cell tumor weighing 34 pounds (15.5 kg.).

Positive physical findings were limited to the presence of a left ovarian tumor and moderate mammary enlargement, with tenderness. Laboratory data were negative.

At operation, Feb. 21, 1921, a solid, left ovarian tumor was found. A frozen section was made rapidly and the unusual character of the neoplasm recognized. Local resection therefore was elected and the patient was given a postoperative course of mild roentgen therapy.

Subsequent correspondence revealed that regular menses became established within four months. The patient went through a normal pregnancy five years later. She is now alive, without recurrence, sixteen years after operation.

Grossly, the specimen consisted of the left tube attached to a solid, encapsulated tumor 5 cm. in diameter. The surface was smooth and grayish brown. On section the mass was solid throughout and of a homogeneously granular texture.

Microscopically, in the capsule were several corpora albicantes and other ovarian remnants. The tumor was composed of small, round, granulosa-like cells with

large basophilic nuclei. The predominant architectural unit was "cylindroid" with transitions to the "folliculoid" and "diffuse" types of Robert Meyer. The tube gave evidence of chronic inflammatory thickening.

CASE 3.—A white multipara, aged 50 years, registered at the clinic June 30, 1931. Her family and personal histories had been negative. Menses had been regular until her climacterium at the age of forty years. One year prior to her registration menses apparently recurred; the bleeding, which occurred monthly, was profuse. Weakness and loss of 10 pounds (4.5 kg.) in weight, completed her list of complaints.

Positive physical findings were an enlarged uterus and a right ovarian tumor. Laboratory data were negative.

At operation, July 3, 1931, hysterectomy was performed, with removal of both adnexa for a right ovarian tumor. The postoperative course was smooth and, follow-

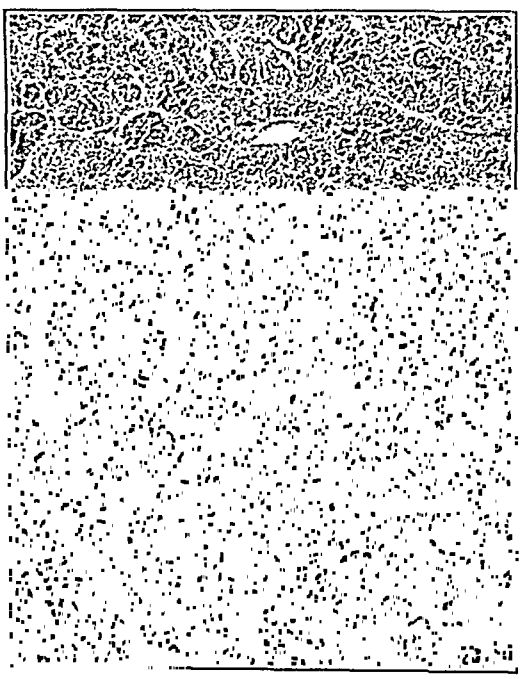


Fig. 2.



Fig. 3.

Fig. 2.—(Case 1.) The general "cylindroid" unit of cellular arrangement. (×80.)
Fig. 3.—(Case 1.) The granulosa-like character of the tumor cells. (×720.)

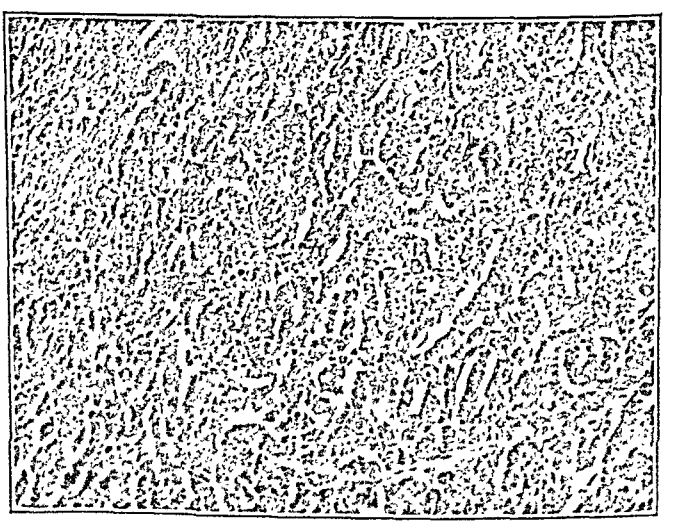


Fig. 4.—(Case 3.) The "moire-silk" pattern of tumor architecture. (×125.)

ing a short period of roentgen therapy, the patient returned home. In follow-up studies this case is classified as a "five-year cure."

The uterus was markedly hypertrophied, measuring 9 by 7 by 5 cm. It contained multiple small fibroids and the endometrium was polypoid. Both tubes were chron-



Fig. 5.



Fig. 6.

Fig. 5.—(Case 8.) An almost pure "folliculoid" type of cell pattern. (×40.)
Fig. 6.—(Case 9.) A mixed "folliculoid" and "cylindroid" type of cell pattern. (×120.)



Fig. 7.



Fig. 8.

Fig. 7.—(Case 9.) Several "follicles" containing "ovum-like" bodies. (×310.)
Fig. 8.—(Case 17.) Three different types of cell architecture in the same field. (×125.)

ically inflamed. The left ovary was fibrocystic and atrophic. The right ovary was replaced by a tumor, 19 cm. in diameter, and of a gross character similar to that described for the previous cases. Regions of cystic degeneration were present on section.

Microscopically the "cylindroid" pattern predominated, illustrating the so-called moire-silk modification. The endometrium was proliferative in type, contained cysts and reflected the action of estrin (Fig. 4).

CASE 4.—A white nullipara, 37 years of age registered Oct. 15, 1912. Family and personal histories were negative. Menses had begun at the age of fifteen years and had been regular for ten years. Following this, for a period of twelve years, menses had been irregular and there had been a tendency toward hypomenorrhea. During the year prior to registration the patient had menstruated only three times.

Examination revealed a large, movable tumor in the cul-de-sac. At operation, Oct. 17, 1912, a local procedure was carried out for removal of a left ovarian tumor.

After operation normal menstrual regularity became established and was maintained for sixteen years. At a recent examination, twenty-three years after the original operation, this patient was in good health.

Grossly, the tumor was a solid, encapsulated neoplasm measuring 10 by 10 by 9 cm. Here again the appearance of the tumor suggested the correct diagnosis.

Microscopically the picture was that of a granulosa cell neoplasm of the mixed folliculoid and cylindroid patterns.

CASES 5 TO 30.—These are summarized in Table I (Figs. 5 to 8).

TABLE I. DATA ON PATIENTS WITH GRANULOSA CELL TUMOR* (PATIENTS MORE THAN 50 YEARS OF AGE)

CASE	AGE	NUMBER OF PREGNANCIES	SYMPTOMS	DURATION SYMPTOMS	PATHOLOGIC FINDINGS		OUTCOME
					FIBROIDS	CYSTIC ENDOMETRIUM	
1	63	2	Periodic bleeding	10 years	+	+	Living, 6 years
2	72	4	Bleeding	2 weeks	0	+	Died, 5½ years later‡
3	60	0	Periodic bleeding	3 months	+	+	Living, 6 years
4	60	4	Periodic bleeding	3 months	0	+	Living, 8½ years
5	70	0	Periodic bleeding	4 years	0†	–	Living, 4½ years
6	58	3	Continuous bleeding	6 months	+	+	Living, 10 years
7	61	1	Irregular spotting	20 years	+	+	Living, 3½ years
8	51	0	Periodic bleeding	1½ years	+	+	Living, 9 years
9	55	0	Periodic bleeding	4 years	+§	+	Died, 10 months later
10	62	1	Periodic spotting	5 years	0	+	Died, 10 days later
11	59	0	Irregular bleeding	5 years	0†	–	Living, 7 years
12	58	3	Irregular and periodic bleeding	4 years	0	+	Living, 17 years
13	56	4	Menorrhagia and metrorrhagia	1 year	0	+	Not traced
14	69	3	Slight irregular bleeding	3 years	0	+	Living, 15 years
15	77	2	Bronchial pneumonia	1 week	0	+	Necropsy
16	61	10	Bleeding	1 month	0	+	Living, 10 years
17	62	5	Recurrent periodic bleeding	8 months	+	+	Living, 11 years

*With the exception of Case 15 in which operation was not performed, all patients were subjected to total abdominal hysterectomy and bilateral salpingo-oophorectomy.

†Carcinoma of fundus uteri.

‡Died of unknown cause.

§Died of cerebral hemorrhage.

COMMENT ON CASES

The average age of these patients was 51 years; the extremes were 17 and 77 years. Eighteen patients, or 60 per cent, were in the postmenopausal age, four were in what might be termed the "menopausal" age of 40 to 50 years, while 30 per cent were in the period of fertility. Marriage and pregnancy did not appear to bear any constant relation to the incidence of tumor development. Of the 28 married patients, 22 had been pregnant one time or more. On the other hand, that the tumors produced temporary sterility was evidenced by the fact that in no case did pregnancy ensue in the interval between the onset of symptoms and the time of operation. That this period of sterility was temporary is illustrated by Case 2, wherein a local operative procedure was followed by normal pregnancy.

Abnormal menstrual manifestations were present in 27 of the 30 cases. In the postmenopausal age, bleeding was the presenting symptom in 16 of the 18 cases. This symptom alone had been periodic in 12 cases, for periods varying from two weeks to twelve years. In several instances

TABLE II. DATA ON PATIENTS WITH GRANULOSA CELL TUMOR (PATIENTS 40 TO 50 YEARS OF AGE)

AGE	NUMBER OF PREGNANCIES	SYMPTOMS	DURATION SYMPTOMS	OPERATIVE PROCEDURE	PATHOLOGIC FINDINGS		OUTCOME
					FIBROIDS	CYSTIC ENDOMETRIUM	
48	2	Menorrhagia	5 years	Local†	–	–	Not traced
50	2	Menorrhagia	1 year	2 local operations	–	–	Recurrence?
40	0	Amenorrhea	1 year +	Total*	0	+	Living, 8 years
47	3	Amenorrhea and menorrhagia	2 years	Total	+	+	Living, 5 years

*Total abdominal hysterectomy and bilateral salpingo-oophorectomy.
†Operative resection of tumor only.

TABLE III. DATA ON PATIENTS WITH GRANULOSA CELL TUMOR (PATIENTS LESS THAN 40 YEARS OF AGE)

AGE	NUMBER OF PREGNANCIES	SYMPTOMS	DURATION SYMPTOMS	OPERATIVE PROCEDURE	PATHOLOGIC FINDINGS		OUTCOME
					FIBROIDS	CYSTIC ENDOMETRIUM	
33	1	Amenorrhea Menorrhagia	2 years 1 year	Local†	–	–	Died, 3 days p.o.
38	5	Amenorrhea and menorrhagia	5 years	Total*	0	+	Living, 9 years
25	1	Amenorrhea Metrorrhagia	18 mo. 3 mo.	Total	+	+	Living, 9 years
17	0	Amenorrhea	1 year	Local	–	–	Living, 2 years
26	1	Constant flow	1 year	Local	–	–	Living, 20 years

*Total abdominal hysterectomy and bilateral salpingo-oophorectomy.
†Operative resection of tumor only.

the patients described these episodes as being accompanied by the manifestations of "normal" menstruation such as uterine cramps, tenderness of the breasts, and low backache.

In the menopausal age amenorrhea of long or of short duration usually was followed by recurrence of vaginal bleeding, again periodic. In one of the cases amenorrhea and menorrhagia occurred alternately over a period of two years.

In the group of cases in which the patients were less than forty years of age, amenorrhea was a symptom of unusual frequency; it occurred in seven instances. In Case 1, amenorrhea (except for occasional spotting) had been present for twelve years and antedated by four years the appearance of palpable pelvic tumor. Amenorrhea followed by bleeding was a feature in two cases. Menorrhagia and metrorrhagia were present in one instance. Of the patients in this group who underwent local resection of the tumor, all except one experienced a return of normal menses following operation.



Fig. 9.—(Case 24.) The "Swiss cheese" type of endometrium found in connection with granulosa cell tumors. (×125.)

Little need be said of the physical findings in these cases. An enlarged uterus was recognized in the majority of instances and a palpable adnexal tumor in most of the cases. Clinical anemia was present in those cases in which the patients suffered from menorrhagia and metrorrhagia. Evidence of hyperthyroidism was observed in two instances; this raises a question of a possible etiologic relationship between hyperthyroidism and the ovarian tumor.

The neoplasms were unilateral in every case although in one instance, there was a small dermoid cyst involving the contralateral ovary. Ascites was noted in one of the cases but metastasis was not observed in any. Adhesions usually were absent but on two occasions were found to be extensive and associated with tumors which had become twisted on their pedicles.

Among older patients hysterectomy, with bilateral salpingo-oophorectomy, was the usual procedure, while among younger patients a

more conservative type of operation was elected. In eight instances local resection of the tumor was carried out. Postoperative irradiation was given in approximately 60 per cent of the cases.

Seventeen uteri were available for study. Hypertrophy was a definite feature in 14 cases. Leiomyomas, usually multiple, were present in 8 cases. Endometrial carcinoma was present in two cases and this again raises the question of its possible relation, etiologically, to ovarian neoplasm. In all of the remaining 15 of the 17 cases there was present a condition of polypoid-cystic change, with a definite Swiss-cheese pattern in 9 (Fig. 9).

The contralateral ovary was available for study in 17 instances. Absence of mature or maturing corpora lutea represented the only constant finding. A mild degree of follicular hyperplasia was present in two instances. One ovary was the seat of a small dermoid cyst but no example of a second granulosa cell tumor could be found.

Changes in the Fallopian tubes were not remarkable.

The incidence of malignancy in this series of cases is perhaps lower than the average for reported cases of granulosa cell tumors. One of the patients who is living has a definite, inoperable recurrent growth. Two of the patients we have been unable to trace. Two patients who had large tumors died from postoperative complications but metastasis could not be demonstrated. The remaining 25 patients are living and well, without recurrence, at periods of from two to thirty years after operation. Case 1 is illustrative of a granulosa cell tumor of a known duration of eight years. The tumor attained a weight of 34 pounds (15.5 kg.) without metastasizing. This patient is now alive twenty-two years after local resection of her tumor, followed by a course of mild roentgen therapy.

SUMMARY, CONCLUSIONS AND A SUGGESTION

1. The clinical and pathologic features of 30 granulosa cell neoplasms are presented.

2. These tumors are thought to arise from granulosa cell rests in the hilus of the ovary, or from degenerating Graafian follicles.

3. The tumor cell unit anatomically and functionally resembles the granulosa cell.

4. Folliculoid, cylindroid, and diffuse tumor cell patterns represent varying degrees of differentiation rather than separate entities.

5. A pathologic report of proliferative endometrium with cysts in a case of periodic, postmenopausal bleeding, should demand exploratory laparotomy even in the absence of a palpable pelvic tumor.

6. Granulosa cell tumors appear to be of a low grade of malignancy. The suggestion is made therefore that surgical procedures employed in the treatment of these tumors be conservative when the patients are young.

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A FIFTEEN-YEAR STUDY OF CESAREAN SECTION IN THE WOMAN'S HOSPITAL IN THE STATE OF NEW YORK*

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IN THE fifteen-year period from Jan. 1, 1923, to Jan. 1, 1938, 20,127 women, in the viable period of pregnancy, have been delivered in the Woman's Hospital in the State of New York. In this group are all deliveries at or beyond the twenty-eighth week of gestation. There were 9,712 of these women who were on the Ward Obstetrical service and 10,415 were private patients. There were 94 maternal deaths or an uncorrected maternal mortality of 0.46 per cent, with an uncorrected fetal mortality of 4.3 per cent. This includes stillbirths and neonatal deaths from all causes while the baby remained in the hospital. Prematurity or major deformities incompatible with life were the causative factors in nearly 60 per cent of these stillbirths and neonatal deaths.

The following is a review of the cesarean sections performed in these 20,127 delivered women. In the fifteen-year period covered by this study the obstetric ward service has been under the direction of ten attending and junior attending surgeons with their adjuncts and assistants. Approximately two-thirds of the private obstetric patients in the series have been delivered by this group of obstetricians, while the remaining one-third of the private obstetric patients have been delivered by a selected courtesy group of some 25 obstetric and gynecologic specialists.

Approximately 4,000 women in the 20,127 had some operative delivery other than prophylactic or low forceps, an operative incidence of 1:5 deliveries. This high incidence of operative interference is perhaps due to the fact that our facilities are limited and on the ward service preference is given to the admission of primiparas or to multiparas who have abnormalities or previous obstetric difficulties. On the private service are numerous consultants to whom are referred many patients who are considered abnormal by the general practitioner. In other words the material for study contains a higher incidence of abnormalities and obstetric complications than is encountered in general obstetric practice.

Approximately 800 in each 1,000 deliveries terminated spontaneously or by the use of prophylactic low forceps. In other words, 200 in each 1,000 women or 4,000

*Presented at a meeting of the New York Obstetrical Society, May 10, 1938.

in the total group of 20,127 delivered women, required assistance. In the slightly more than 16,000 spontaneous or prophylactic low forceps deliveries there were 32 deaths, a maternal mortality rate of 0.2 per cent, while in the 4,000 who had indicated operative deliveries there were 62 maternal deaths, a maternal mortality rate of 1.5 per cent. Spontaneous delivery, or prophylactic low forceps delivery in the hands of obstetric specialists, is the safest for both mother and baby. In this series the use of prophylactic low forceps was followed by better results to both mother and baby.[1] Mid- and high forceps deliveries (the high forceps operation being used very rarely) gave the next lowest maternal mortality, the maternal mortality being 17 deaths in 2,000 or approximately 0.81 per cent with total fetal mortality of 6 per cent, in these vaginal deliveries. Breech extraction or version and breech extraction had the highest maternal and fetal mortality rates. In 980 such deliveries the maternal death rate was 1.69 per cent while the fetal death rate was 20 per cent.

Some years ago in our follow-up of the delivered patients on the ward service we felt that our results in the more difficult vaginal deliveries were not entirely satisfactory. In the prolonged labors and difficult vaginal operative deliveries, we found a rather high incidence of birth injuries, stillbirths, and neonatal deaths. In addition the incidence of pelvic floor injury, cystocele, rectocele, and uterine prolapsus was not encouraging. We felt that many of these women would be faced with subsequent partial invalidism and later plastic operations with an additional risk to health and life. At this time the low flap cesarean section was being popularized. The advantages of this operation appealed to us and we began using it more frequently in the borderline cases usually after a trial labor. The results were so satisfactory that the method has been adopted as the operation of choice in all cesarean sections on the ward service and our indications for its use have been widened to include many of the so-called relative indications for cesarean section.

Cesarean section has not been in competition with spontaneous delivery or with delivery by prophylactic or low forceps. It has been in competition with the more difficult forceps operations and with breech extraction and version and breech extraction especially when labor was unduly slow or in the presence of moderate degrees of pelvic deformity or other obstetric and general complications.

Comparative incidence rates of cesarean section are shown in Table I.

TABLE I. COMPARATIVE INCIDENCE AND MORTALITY TABLES ON CESAREAN SECTION

			INCIDENCE	MORTALITY RATE
Fraser	1938	Montreal	1:44	3.0
Greenhill*	1930	Chicago	1:48	—
Skeel-Jordan	1932	Cleveland	1:44	7.15
Monhaupt	1932	Germany	1:45	—
Johnson and Smith	1931	Houston	1:36	14.4
Palmer	1934	Akron	1:41	4.5
Maxwell	1934	U. of Calif. Hosp.	1:21	3.0
Margeson	1929	Boston City Hosp.	1:29	3.4
Hawkes	1929	N. Y. Nurs. & Child's	1:62	3.6
Irving	1935	Boston Lying-in	1:35	3.1
	1938	Woman's Hospital	1:22	2.96

*Quoted by Fraser.

Our incidence of cesarean section is higher but our mortality rate is somewhat lower than average. I believe the general mortality rate of cesarean section is considered to be about 6 to 10 per cent. Certainly it will run considerably higher in the less well-equipped hospitals and in the hands of unskilled or occasional operators.

The number and incidence rate of cesarean section at the Woman's Hospital is shown in Table II. The incidence rate of cesarean section is consistently higher in the private patient group, general average on ward patients 1:29, private 1:18. The incidence rate of the past five or six years in the private group is unusually

TABLE II. NUMBER AND INCIDENCE OF CESAREAN SECTIONS, WARD AND PRIVATE CASES, BY YEARS, 1923-1937

	TOTAL DELIVERIES			CESAREAN SECTIONS			INCIDENCE OF CESAREAN SECTIONS		
	TOTAL	WARD	PRIVATE	TOTAL	WARD	PRIVATE	TOTAL	WARD	PRIVATE
1923	1,089	548	541	23	1	22	1:47	1:548	1:25
1924	1,197	537	660	23	8	15	1:52	1:67	1:44
1925	1,280	513	767	38	9	29	1:34	1:57	1:26
1926	1,329	527	802	32	11	21	1:42	1:48	1:38
1927	1,367	534	833	31	6	25	1:44	1:89	1:33
1928	1,315	536	779	27	7	20	1:49	1:77	1:39
1929	1,411	550	861	49	15	34	1:29	1:37	1:25
1930	1,377	586	791	46	24	22	1:30	1:24	1:36
1931	1,334	624	710	64	24	40	1:21	1:26	1:18
1932	1,422	741	681	80	35	45	1:18	1:21	1:15
1933	1,317	758	559	85	43	42	1:15	1:18	1:13
1934	1,330	771	559	88	34	54	1:15	1:23	1:10
1935	1,433	853	580	107	44	63	1:13	1:19	1: 9
1936	1,405	809	596	120	46	74	1:12	1:18	1: 8
1937	1,521	825	696	99	31	68	1:15	1:27	1:10
15 years	20,127	9,712	10,415	912	338	574	1:22	1:29	1:18

high. Perhaps good results with cesarean section has blinded us to the possibility of success by vaginal delivery in a certain number of this group.

Absolute indications for cesarean section are few. Pelvic deformity or contraction of such degree that the delivery of a child is impossible even after crushing or craniotomy, would be such an indication as would fixed tumors blocking the pelvis to an equal degree. All other indications must be considered as relative, since it would be possible to deliver the fetus, either dead or alive, through the birth canal, though at a terrific sacrifice in fetal life and the risk of excessive damage and permanent invalidism to the mother.

TABLE III. CHIEF INDICATIONS FOR CESAREAN SECTION

	TOTAL	WARD	PRIVATE
Abnormal pelvis	401	165	236
Previous cesarean section	191	77	114
Disproportion	146	50	96
Large baby	71	17	54
Toxemia	102	54	48
Eclampsia	5	1	4
Previous stillbirth and difficult delivery	190	74	116
Elderly primiparas	87	27	60
Cervical dystocia	235	85	150
Inertia uteri	32	8	24
Previous myomectomies	30	7	23
Breech presentation	43	18	25
Abnormal presentation	36	14	22
Tuberculosis	38	16	22
Tumor blocking pelvis	15	6	9
Placenta previa	75	33	42
Premature separation of placenta	22	7	15
Previous plastic repair	34	5	29
Myomas	36	10	26
Cardiac disease	60	34	26
Thyrotoxicosis	5	3	2
Psychoses	6	-	6
Attempted vaginal delivery	8	2	6
Bandl's ring	5	4	1
Maternal exhaustion	17	9	8
Prolonged sterility	15	2	13
Desire for sterilization	6	6	-

In the woman with a moderate pelvic deformity or disproportion or with complicating mild cardiac or other disease it may be entirely safe to allow a carefully supervised trial labor. If reasonable progress is made without undue maternal exhaustion or evidence of cardiac failure, this trial may go on to the real test of labor as defined by Williams[13]—this test being two hours of full dilatation with ruptured membranes and good uterine contractions. This to my mind is a purely mechanical test of whether the head will go through the pelvis and if the maternal organism will stand the strain of the process. Undue prolongation of labor with inefficient uterine contractions and slow dilatation of the cervix or premature rupture of the membranes markedly increases the risks to both mother and baby whatever the type of eventual delivery.

The chief indications for which cesarean section was done in this series are shown in Table III. It will be seen that many patients had more than one indication. The totals on the chart indicate the number of patients presenting a given indication.

Table IV gives a brief résumé of the obstetric history of our cesarean section patients to which is added the uncorrected fetal mortality table for all cesarean deliveries. The mortality rate of 2.62 compares favorably with the general mortality rate of 2.96. The majority of these patients had elective cesarean section without trial labor. Those patients having the third cesarean section had more than double the average mortality rate. The series is small and no conclusions are drawn.

TABLE IV. OBSTETRIC HISTORY OF PATIENTS

	NO. OF CASES	MATERNAL DEATHS		INFANT DEATHS		STILL-BIRTHS		TOTAL FETAL MORTALITY	
		NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
Total	912	27	2.96	31	3.40	30	3.29	61	6.69
Primiparas	517	15	2.90	14	2.71	16	3.09	30	5.80
Multiparas	395	12	3.04	17	4.30	14	3.54	31	7.84
With previous cesarean sections*	191	5	2.62	5	2.62	5	2.62	10	5.24
1 previous cesarean	163	3	1.84	5	3.07	4	2.45	9	5.52
2 previous cesarean sections	26	2	7.69	-	-	1	3.85	1	3.85
3 previous cesarean sections	2	-	-	-	-	-	-	-	-
With previous vaginal delivery	204	7	3.43	12	5.88	9	4.41	21	10.29

*With or without previous vaginal deliveries also.

Table V gives the age of patients having cesarean section. The most favorable age group seemed to be in the second decade. In the small group of patients over 40 years of age, the maternal mortality rate, as well as the fetal mortality rate, was more than doubled. This study would indicate that the risk to both mother and baby is markedly increased in patients of 40 years or over.

TABLE V. AGE OF PATIENTS

	ALL CASES			PRIMIPARAS			MULTIPARAS		
	NO. OF CASES	MATERNAL DEATHS		NO. OF CASES	MATERNAL DEATHS		NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE		NO.	RATE		NO.	RATE
All ages	912	27	2.96	517	15	2.90	395	12	3.04
Under 20 years	9	-	-	8	-	-	1	-	-
20-29 years	380	6	1.58	245	4	1.63	135	2	1.48
30-39 years	434	17	3.92	206	8	3.88	228	9	3.95
40 years and over	39	3	7.69	27	2	7.41	12	1	-
Not specified	50	1	2.00	31	1	3.23	19	-	8.33

Table VI shows the maternal and infant mortality rate according to the period of gestation.

TABLE VI. PERIOD OF GESTATION

	ALL CASES	28-38 WEEKS	38-40 WEEKS	OVER 40 WEEKS
No. of cases	912	168	693	51
Maternal deaths	27	2	20	5
Rate	2.96	1.19	2.89	9.80
Infant deaths	31	21	9	1
Rate	3.40	12.50	1.30	1.96
Stillbirths	30	11	15	4
Rate	3.29	6.55	2.16	7.84
Total fetal mortality	61	32	24	5
Rate	6.69	19.05	3.46	9.80

Between twenty-eight and thirty-eight weeks of gestation the maternal death rate was low but the fetal mortality was 3 or 4 times the general average. In gestation beyond forty weeks, there was a high maternal death rate, nearly 4 times the average for the total group and the fetal death rate was about twice the general average.

Table VII summarizes the maternal deaths with reference to the time of rupture of the membranes.

TABLE VII. CONDITION OF MEMBRANES

	NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE
All cases	912	27	2.96
Membranes intact	622	15	2.41
Membranes ruptured	290	12	4.14
Less than 12 hours	116	5	4.31
12-24 hours	54	-	-
24 hours and over	73	7	9.59
Time not recorded	47	-	-
Premature rupture	37	3	8.11

In the large group of women with intact membranes at the time of cesarean section, the maternal death rate was below the average while the maternal death rate in those in whom the membranes were ruptured at the time of operation, the general maternal mortality was nearly double. When membranes had been ruptured for over twenty-four hours at the time of cesarean section, the maternal mortality rate was tripled. An interesting finding is the absence of any maternal deaths in a group of 54 women with ruptured membranes of between twelve and twenty-four hours. This may be due to the fact that these are uncomplicated cases in which a carefully supervised trial labor was attempted.

Table VIII reviews the maternal death rate in relation to the dilatation of the cervix.

TABLE VIII. CONDITION OF CERVIX

	NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE
All cases	912	27	2.96
Undilated	543	12	2.21
Dilated	365	14	3.84
Less than 5 cm.	215	8	3.72
5-9 cm.	107	5	4.67
9 cm. and over (fully)	32	1	3.13
Amount not recorded	11	-	-
No cervix	4	1	25.00

It would seem that cervical dilatation had only moderate effect in increasing the death rate, although as full dilatation was approached, the maternal death rate was considerably above the average for the total group.

Table IX summarizes both the maternal and fetal mortality in relation to the duration of labor before the cesarean section was done.

TABLE IX. DURATION OF LABOR

	NO. OF CASES	MATERNAL DEATHS		INFANT DEATHS		STILLBIRTHS		TOTAL FETAL MORTALITY	
		NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
All cases	912	27	2.96	31	3.40	30	3.29	61	6.69
No labor	457	11	2.41	25	5.47	13	2.84	38	8.31
After period of labor	455	16	3.52	6	1.32	17	3.74	23	5.05
Less than 6 hours	56	4	7.14	3	5.36	2	3.57	5	8.93
6-24 hours (incl.)	242	4	1.65	2	0.83	10	4.13	12	4.96
Over 24 hours	140	8	5.71	-	-	5	3.57	5	3.57
Time not recorded	17	-	-	1	5.88	-	-	1	5.88

In general the death rate is higher in those women having cesarean section after a period of labor as compared to the group who were cesareanized prior to the onset of labor. The fact that many of our more serious ante-partum complications such as placenta previa, toxemia, tuberculosis, and the more severe grades of cardiac disease were sectioned before labor, brings the death rate in total group of elective section to about the average figure. If these severe ante-partum complications are left out, the elective section group shows a very low death rate of approximately 1 per cent. In this series it would be possible to pick up several groups of 75 to 100 or more consecutive elective cesarean sections done in otherwise healthy women, without any maternal deaths. The low maternal mortality in the group of women having cesarean section after from six to twenty-four hours of labor, is again perhaps best explained on the grounds that these were otherwise healthy women in whom a carefully supervised trial labor was allowed. In the group of women who had twenty-four hours or more of labor, there was a rapid rise in maternal mortality.

Table X is a summary of the type of anesthesia used for cesarean section.

TABLE X. TYPE OF ANESTHESIA USED

	NO. OF CASES	MATERNAL DEATHS	
		NO.	RATE
Total	912	27	2.96
Inhalants	833	23	2.76
Gas, oxygen, ether	784	23	2.93
Ether	26	-	-
Gas, oxygen	19	-	-
Ethylene	1	-	-
Ether, chloroform	1	-	-
Chloroform	1	-	-
Chloroform and gas, oxygen, ether	1	-	-
Spinal	72	4	5.56
Alone	56	3	5.36
With inhalants	16	1	6.25
Local	3	-	-
Alone	1	-	-
With inhalants	2	-	-
Avertin	4	-	-
Alone	2	-	-
With inhalants	2	-	-

Practically all cesarean sections were done under inhalation anesthesia, usually gas, oxygen, and ether combination. Spinal anesthesia had the highest maternal mortality rate, though none were directly due to the anesthesia itself. Spinal anesthesia was used more frequently in the severely toxic cases or in mothers with known pulmonary

disease. The pulmonary complications in women having spinal anesthesia were comparable to those receiving inhalation anesthesia.

Table XI indicates the marked preference of the low flap cesarean especially in the ward service.

TABLE XI. WARD AND PRIVATE CASES BY TYPE OF CESAREAN SECTION

	TOTAL CASES	WARD		PRIVATE	
		NO.	PER CENT	NO.	PER CENT
Total cesarean sections	912	338	37.1	574	62.9
Low flap	620	253	40.8	367	59.2
Transverse incision	534	220	41.2	314	58.8
Vertical incision	75	28	37.3	47	62.7
Incision not specified	11	5	45.5	6	54.5
Classical	235	51	21.7	184	78.3
Latzko	34	23	67.6	11	32.4
Porro	17	9	52.9	8	47.1
Peritoneal exclusion	6	2	33.3	4	66.7

The transverse incision is highly favored for this operation. It is our belief that the bleeding is less with this incision and the danger of bladder or upper uterine segment involvement from extension of the incision avoided. In our series there has been only one bladder injury with this operation and this was in a patient on whom a vertical incision was made.

In the Latzko operation, accidental bladder injury occurred four times. In three of these the bladder was opened and in one the musculature only was damaged sufficiently to require repair. All of these patients healed well without complication referable to the bladder injury. In one of the Latzko operations, done after a prolonged labor, in a woman who had fever and a high Bandl's ring, there was an accidental injury to the ureter, apparently from disturbance with the blood supply, since she developed a ureterocervical fistula on the seventh day. This required subsequent operation about ten months later following which there has been no further urinary leakage. The uterovesical fold of peritoneum was accidentally opened 6 times in the Latzko operations. And, in 4 other patients this fold was deliberately incised and closed before opening the uterus, as recommended by Aldridge.[13] In no case did this opening result in peritonitis.

In the Porro operations there was one ureteral injury which was repaired by transplant of the ureter into the bladder with complete recovery and good kidney function.

In the total group of 912 cesarean sections there were 165 incidental operations exclusive of the hysterectomies which, of course, were a part of the Porro operations. Forty of these patients had myomectomies, 114 had sterilization either by partial excision of the tubes or ligation of tubes. In recent years ligation by the Pomeroy method has been favored. One patient had an ovarian cyst removed at time of the section, and six had unilateral salpingo-oophorectomy. Only one patient had an associated appendectomy.

It has been a general policy to do as little operating as possible in association with cesarean sections. Bilateral ligation of the tubes seemed to add little to the morbidity or mortality. Since only 3 patients in the 165 who had additional operation with cesarean section died, our mortality rate was not increased.

One patient died after cesarean section plus myomectomy.

One patient died after cesarean section plus sterilization.

One patient died after cesarean section plus sterilization and myomectomy.

Table XII shows the mortality and morbidity associated with various types of cesarean section.

Low flap cesarean section had less than half the mortality of the classical section. Latzko section had a mortality equal only to the average mortality of the whole series. The Porro naturally had higher than average mortality rate due to the complications which indicate this type of operation. The peritoneal exclusion operation was done in a very small series and to my mind the maternal mortality rate shown here is not a fair indication of the worth of this operation in the presence of indications for its use.

TABLE XII. MORTALITY AND MORBIDITY BY TYPE OF CESAREAN SECTION

	NO. OF CASES	MATERNAL DEATHS		MATERNAL MORBIDITY	
		NO.	RATE	NO.	RATE
All types	912	27	2.96	277	30.37
Low flap	620	13	2.10	168	27.10
Classical	235	10	4.26	80	34.04
Latzko	34	1	2.94	19	55.88
Porro	17	1	5.88	8	47.06
Peritoneal exclusion	6	2	33.33	2	33.33

TABLE XIII. CHIEF CAUSES OF POST-PARTUM MORBIDITY

	CASES
Post-partum morbidity, all causes	277*
Sapremia	55
Unexplained temperature rise	38
Toxemia	4
Eclampsia	3
Septicemia	7
Metastatic abscesses	4
Parotitis	6
Pelvic sepsis, localized	18
Urinary infections	43
Urinary fistula	4
Peritonitis, general	6
Paralytic ileus	7
Hemorrhage and sec. anemia	34
Shock, post partum	4
Mastitis	26
Faulty wound union	43
Evisceration	1
Vascular disturbances	38
Heart conditions	9
Respiratory complications	31
Other complicating diseases	8

*One hundred twenty-one of these cases had ante-partum morbidity also.

Table XIII tabulates the major causes of post-partum morbidity associated with cesarean section. The accepted criteria for morbidity in this series has been a temperature of 100.4° F. on any two successive days after the first forty-eight hours postoperative. Also included in morbidity tables are faulty wound healing, urinary complications and various constitutional diseases. It will be noted that in the total group of 277 postcesarean morbid patients, 121 also had ante-partum morbidity.

Table XIV gives a summary of patients dying after cesarean section, showing the period of gestation, the incidence of previous cesarean sections, and also the type of examination made prior to a cesarean section.

TABLE XIV. SUMMARY OF DEATH CASES

	LOW FLAP	CLASSICAL	PERITONEAL EXCLUSION	PORRO	LATZKO
Vaginal and Rectal Examinations					
No examination	2	8	-	-	-
Rectal examination only	1	-	-	-	-
Vaginal examination only	5	2	1	1	-
Rectal and vaginal exam.	5	-	1	-	1
Period of Gestation					
30-36 weeks	1	1	-	-	-
38-40 weeks	7	9	2	1	1
Over 40 weeks	5	-	-	-	-
Previous Cesarean Sections					
	1	4	-	-	-

It will be noted that in 8 patients on whom no vaginal or rectal examination was made, there was death following classical cesarean section, while only 2 patients on whom no vaginal or rectal examinations were made, died subsequent to a low flap cesarean section.

This table also shows the rise in death rate in the post-mature patient. Five patients died who had had previous cesarean section, a mortality rate slightly over 2½ per cent or a little less than the general mortality rate for the whole series. It would seem that repeated cesarean section is no more dangerous than the primary cesarean section.

Table XV shows a tabulation of patients dying following cesarean section, classified as to the condition of the membranes and the duration of labor.

TABLE XV. SUMMARY OF DEATH CASES

	LOW FLAP 620	CLASSICAL 235	PERITONEAL EXCLUSION 6	PORRO 17	LATZKO 34
Condition of Membranes					
Membranes intact	4	9	2	-	-
Rupt. less than 12 hours	4	-	-	1	-
12-24 hours	-	-	-	-	-
24 hours and over	5	1	-	-	1
Duration of Labor					
No labor	2	9	-	-	-
Less than 12 hours	2	1	1	1	-
12-24 hours	1	-	-	-	-
24 hours and over	8	-	1	-	1

This table shows the superiority of low flap over classical cesarean section even with intact membranes. Again it shows the increased number of deaths after twenty-four hours of ruptured membranes. The best results are in the twelve- to twenty-four-hour group. This represents the group who were allowed a reasonable trial labor and in whom none of the major ante-partum complications were present. Also the increase in deaths after twenty-four hours of labor even though low flap section is chosen.

Table XVI gives a summary of the ante-partum complications and the causes of death in the 27 fatalities following 912 cesarean sections.

TABLE XVI. SUMMARY OF CAUSES OF DEATH

	LOW FLAP (620)	CLASSICAL (235)	PERITONEAL EXCLUSION (6)	PORRO (17)	LATZKO (34)
Peritonitis	3	1	-	1	-
Septicemia	1	3	2	-	-
Pulmonary embolism	3	-	-	-	-
Cerebral embolism	-	1	-	-	-
Mesenteric thrombosis	-	1	-	-	-
Coronary thrombosis	-	-	-	-	1
Myocardial failure	3	-	-	-	-
Hemorrhage and shock	1	3	-	-	-
Pneumonia	1	1	-	-	-
Collapse of lung	1	-	-	-	-
Ante-partum Complications					
Placenta previa	2	-	-	-	-
Toxemia	3	3	1	1	-
Cardiac disease	2	1	1	-	-
Sec. anemia	1	-	-	-	-
Tuberculosis	1	-	-	-	-
Acute yellow atrophy	1	-	-	-	-

Thirteen deaths followed the low flap operation done on 620 patients, 10 deaths followed the classical operation done on 235 patients. In the 13 deaths following the low flap operation, 5 are from causes directly traceable to the operation, the remaining 8 are from complications not directly connected with the type of delivery. While in the 10 deaths following the classical cesarean, 8 are from causes directly traceable to the operation while only two are from complications not directly associated with the type of delivery. The low flap group shows that 10 of the 13 mothers who died had major ante-partum complications which were factors in the fatal outcome while in the classical group only 4 of the 10 mothers who died had associated severe ante-partum complications. The classical operation in itself would seem to be more dangerous than the low flap operation.

Table XVII shows the maternal mortality rate in the group of 20,127 women tabulated by years for both ward and private patients; in addition, the cesarean deaths are likewise tabulated.

TABLE XVII. MATERNAL MORTALITY FOR CESAREAN SECTIONS AND ALL DELIVERIES WARD AND PRIVATE CASES, BY YEARS, 1923-1937

	MATERNAL DEATHS						CESAREAN SECTION DEATHS					
	TOTAL		WARD		PRIVATE		TOTAL		WARD		PRIVATE	
	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE	NO.	RATE
1923	6	0.55	2	0.36	4	0.74	2	8.70	-	-	2	9.09
1924	2	0.17	2	0.37	-	-	-	-	-	-	-	-
1925	5	0.39	3	0.58	2	0.26	3	7.89	1	11.11	2	6.90
1926	7	0.53	3	0.57	4	0.50	2	6.25	1	9.09	1	4.76
1927	9	0.66	4	0.75	5	0.60	2	6.45	-	-	2	8.00
1928	10	0.76	4	0.75	6	0.77	2	7.41	1	14.29	1	5.00
1929	13	0.92	5	0.91	8	0.93	3	6.12	1	6.67	2	5.88
1930	8	0.58	5	0.85	3	0.38	1	2.17	1	4.17	-	-
1931	6	0.45	4	0.64	2	0.28	1	1.56	1	4.17	-	-
1932	7	0.49	3	0.40	4	0.59	3	3.75	1	2.86	2	4.44
1933	5	0.38	3	0.40	2	0.36	-	-	-	-	-	-
1934	3	0.22	2	0.26	1	0.18	2	2.27	2	5.88	-	-
1935	5	0.35	3	0.35	2	0.34	3	2.80	2	4.55	1	1.35
1936	6	0.43	3	0.37	3	0.50	2	1.67	1	2.17	1	1.59
1937	2	0.13	-	-	2	0.29	1	1.01	-	-	1	1.47
15 years	94	0.47	46	0.47	48	0.46	27	2.96	12	3.55	15	2.61

Deaths following cesarean section totaled slightly more than one-quarter of all deaths in the series. However, in two years 1924 and 1933 with two deaths and 5 deaths, respectively, none were due to cesarean section. While in 1927, 1928, 1929, 1930, with a total of 40 deaths, cesarean section was responsible for only 8 deaths; 1929 with the highest maternal mortality of the fifteen years and showing an incidence of cesarean section of 1:29 deliveries, yet only 3 of the 13 deaths followed cesarean section. In 1933 with a cesarean incidence of 1:15 deliveries there were no cesarean deaths although there were 5 maternal deaths following vaginal delivery. In general as the incidence of cesarean section increased there has been no corresponding increase in the maternal death rate. This can be proved by a comparison with the incidence in Table I. In fact the tendency has been to a lower general maternal mortality as the incidence of cesarean increased. This, I believe, is due to the performance of cesarean sections earlier in labor with the avoidance of prolonged labor and maternal exhaustion, in the presence of ruptured membranes or other complicating factors.

Fewer women are being allowed to become exhausted before delivery is made. Another important factor is the more frequent use of blood transfusion and other supportive measures. Blood donors are readily available and in a majority of cases a suitable donor is present in the hospital at the time of the cesarean section. If the hemoglobin and red blood cell counts are low a preoperative transfusion is given. Also patients are now treated for shock and restored to a reasonably fair condition before cesarean section is done. This is noticeably true in the treatment of placenta

previa and the severe degrees of premature separation of placenta with an improved maternal mortality whatever the type of delivery.

The total maternal mortality rate in 1937 is most gratifying. There were no deaths of ward patients in 825 deliveries with 31 cesarean sections.

A comment on the 27 deaths from all causes occurring in 912 cesarean sections may be ventured in no spirit of criticism but in an honest effort to evaluate the results in this long study. Some of the cases are my own. In the 10 deaths following classical cesarean section in 235 operations, there are 6 on which no comment is indicated, if one chooses to employ the classical operation for the elective cesarean section. In 4 of these cases I wish to make certain observations.

1. A patient in the private group on whom classical section was elected after eleven days of ruptured membranes, died of septicemia and peritonitis on the sixth day postoperative, with positive staphylococcus blood culture. This patient might have been safer with an earlier operation or possibly an extraperitoneal operation.

2. A patient in the private group who was treated for three and one-half weeks in the hospital with a blood pressure ranging from 190/100 to 210/130 and albuminuria from 1 to 6 gm. per liter. There was no improvement during this time. A classical section was done at thirty weeks because of a desire for sterilization. There was considerable bleeding and shock though no blood transfusion was given until shortly before death, twenty-four hours postoperative. Possibly an earlier induction of labor when the patient failed to respond to the toxemia treatment might have given a more favorable result.

3. A patient in the private group who had profuse bleeding at the time of the classical section, had uterine tamponade at time of operation. No transfusion until four hours later and the bleeding not controlled. In this case an earlier transfusion followed by repacking or possible hysterectomy might have been considered a better choice of procedure.

4. A private patient on whom an elective classical section was done. This patient had no blood count before operation and none until the fifth day postoperative when a marked anemia of 45 per cent with 2,500,000 red blood cell count was found. Then a 500 c.c. blood transfusion was given. No further blood count recorded and no further transfusion. This patient died on the tenth day of sepsis and abscess of parotid gland. Possibly earlier and more vigorous attention to the anemia might have prevented the lowered resistance and septic condition.

In the 13 deaths following 620 low flap cesarean operations, there are 4 on which no comment is indicated. Comments are made on 9 as follows:

1. A 39-year-old primipara, in the private group, with a myocardial weakness from fatty degeneration, who had sixty hours labor with cervical dystocia and disproportion. This woman died of cardiac and respiratory failure on the operating table. An earlier cesarean section before the exhaustion of labor would seem to be indicated.

2. A ward patient 33 years of age, multipara of 48 weeks' gestation with transverse position. Admitted and examined in the early stages of labor because of moderate vaginal bleeding. Examination by an intern stirred up an uncontrollable vaginal hemorrhage. An obstetrician was called who packed the vagina after a blood loss of approximately 2,500 c.c. Gum glucose was given immediately and a low flap section was done. Eleven-pound baby in good condition. Patient received a blood transfusion during the operation. Patient died one hour later of hemorrhage and shock. Better results might have been expected if this patient had been suspected of a possible placenta previa when she went to forty-eight weeks' gestation with a transverse presentation. Our rule now is no examination of bleeding patients until a donor is ready and then examination only by a member of the attending staff with everything in readiness for operation if indicated. No patient is subjected to cesarean section until she has reacted from her shock through the use of blood transfusions and such other methods as are indicated.

3. Ward patient, para v, forty-two weeks' gestation, thirty-eight-hour trial labor with marked disproportion. Two previous stillbirths. This patient died of peritonitis on her third day. This trial labor was too long for safety even with low flap operation. In view of the history of stillbirths, etc., an elective cesarean section might better have been chosen.

4. Private patient at forty-one weeks' gestation. A medical induction of labor following extensive myomectomies. Sixty-four hours trial labor and temperature of 101° F. followed by low flap cesarean section. Peritonitis and death on fifth day postoperative. The advisability of an induction and prolonged trial labor in a woman with extensive myomectomy wounds, is questionable. No transperitoneal operation is safe after sixty-four hours of labor and in the presence of fever.

5. A ward patient with myocardial disease and a placenta previa. Died six hours postoperative of hemorrhage and shock. Transfusion was not given until more than four hours postoperative. This again demonstrates the advisability of having a donor in attendance at time of operation in all placenta previa cases.

6. A ward patient. This patient had had a previous cesarean section. Her pregnancy was unsupervised. She first presented herself after twenty-four hours of labor plus ruptured membranes. She died on the eleventh day postoperative of peritonitis. She had marked secondary anemia when admitted and received one blood transfusion before operation and three after operation. This death may be charged to the neglect of the patient herself since she delayed placing herself under medical care.

7. A private patient. Treated during pregnancy for mitral stenosis and an elective section was planned. The patient delayed entering the hospital until she had been in labor for ten hours when she had beginning decompensation. She died one hour postcesarean. Again, this may be charged to the patient's negligence, since she had been warned of the dangers and plans had been made for elective section before or at the onset of labor.

8. A ward patient, forty-eight hours in labor with ruptured membranes. Cervical dystocia with head above brim in R.O.P. position. Died on the third day postoperative of peritonitis. The selection of an extraperitoneal section might have been a better choice.

9. A private patient, 35 years old, primipara, at thirty-eight weeks' gestation. Toxemia of pregnancy with early yellow atrophy of liver. Elective low flap section. Patient had central placenta previa not previously suspected. Died six hours postoperative of shock and a moderate retroplacental hemorrhage of 300 c.c., behind the flaps of the operation. Transfusion was of no avail. Autopsy showed fairly advanced yellow atrophy of liver. With the known tendency to oozing and bleeding in cases of yellow atrophy of the liver it might be well to give a preoperative blood transfusion even though there was no anemia.

The greatest problem of obstetrics is in the management of the borderline indications for cesarean section. With intact membranes and an otherwise relatively normal woman, a trial or even real test of labor is comparatively safe. With ruptured membranes, slow cervical dilatation or rigid cervix and maladaptation of the head, the finest of obstetric judgment is needed. There is great danger in delaying the operation in these borderline cases until the mother is exhausted and an easy prey to infection and complications, and the baby likely to succumb, whatever the type of delivery.

To conclude this laborious study and presentation, I can find no fairer expression of my own views on the use and abuse of cesarean section than those of Mellor[14]: "Unquestionably too many cesareans are performed where the method of delivery should have been otherwise especially when the operation is done under adverse conditions and by relatively untrained obstetric surgeons. Poor results in obstetrics are caused most often by the abuse rather than the proper use of obstetric surgery. Watchful waiting is an essential virtue in obstetric management, but look out for criminal procrastination just around the corner."

Since this study includes both private and ward patients, I hereby acknowledge, with thanks, the courtesy of the many obstetricians involved, and of the Chief Surgeon of the hospital, for permission to use this material.

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DISCUSSION

DR. ALBERT H. ALDRIDGE.—Success in the handling of obstetric patients should not be judged entirely by the mortality rate which accompanies a method of delivery. It should also include an estimation of results in patients that survive.

In recent years, good results with low flap cesarean section have encouraged members of the Woman's Hospital staff to adopt this method of delivery for an increasing number of patients who have cardiac disease, the toxemias of pregnancy, tuberculosis, placenta previa and cervical dystocia. Cesarean section has also been chosen for the delivery of certain cases in which the outlook for babies delivered by vagina was definitely problematical. These cases included those with breech presentation in primiparas, especially when the babies were unusually large or the pelves borderline in size; those showing fetal distress during the first stage of labor, and those with evident fetomaternal disproportion and especially those with histories of previous complicated deliveries or unsuccessful pregnancies. The results of suprapubic delivery in all these types of cases as compared to delivery by the vaginal route has convinced us that cesarean section is occasionally justifiable in the interest of the baby as well as of the mother, if cases are carefully selected.

In some of these cases the benefits and safety of cesarean section depend upon application of the method either as an elective procedure or early in labor. This undoubtedly has resulted in the delivery of some cases in the series by cesarean section which might have been safely delivered by vagina.

Material for this study was collected over a period of years during which much experience has been acquired to guide obstetricians in the selection of patients to be delivered by cesarean section; methods for the routine preparation of patients for operation have improved and the technique of cesarean section has been perfected. Unsatisfactory results in the series serve to emphasize the importance of careful selection of patients to be delivered by cesarean section and the necessity of meticulous preparation of patients for operation.

DR. BENJAMIN P. WATSON.—I was especially interested in comparing the results at the Woman's Hospital with our experience at Sloane Hospital, which is very much the same, namely about 3 to 4 per cent cesarean sections in the ward cases.

I entirely agree with all that Dr. Aldridge has said and what Dr. Barrett has said in regard to the prevention of mortality in these cases. We are very likely to believe that cesarean section must be rushed, and as a result we do not take enough time and enough trouble in the preparation of our patients prior to operation.

DR. ALFRED C. BECK.—The general idea that most of us hold is that the mortality from cesarean section ought not to be over 1 per cent, if the right operation is done on the right patient at the right time. We pay too much attention to indications and too little attention to contraindications. If we look over the bad results in the Woman's Hospital series, few as they were, we shall find that cesarean section was definitely contraindicated in certain of them, in that the operation was done after the time when cesarean section no longer should have been done.

DR. WILLIAM E. STUDDIFORD.—In looking up the incidence of sections on the Bellevue service I found it amounted to a little over 2 per cent. I do not think we have had any marked fetal mortality as a result of this because our mortality in term infants year after year has run about 3 per cent. Our total maternal mortality

has varied between 0.3 and 0.4 per cent. I do not believe this would have been influenced much by increasing the number of cesarean sections.

In the past five years we have done about 215 sections at Bellevue Hospital, including a considerable number of hysterotomies on toxic patients in whom no improvement had been seen after conservative treatment. The mortality in this group amounted to 3.2 per cent.

One of the striking things in Dr. Barrett's presentation was the very high percentage of cesarean sections for cervical dystocia. I believe there were 225 of them. That amounts to about one-fourth of the indications for cesarean section.

DR. BARRETT (closing).—To Dr. Beck I would say that I believe our incidence was high and that our mortality was too high. If you follow the table, you will find our mortality rate has come down very materially in the last five years. If we could take that selective group which we consider done at the right time, we would have only 1 per cent. It is when we misjudge the case that we get into trouble.

Dr. Studdiford mentioned the high incidence of cervical dystocia. I expected that comment. Cervical dystocia was, however, not the only reason for doing cesarean section in these cases. There are many patients who have disproportion and progress very slowly in labor because of malposition or high occipitoposterior position, who do not engage well and who after a long period of labor have an undilated cervix. These we have come to regard, both in the ward and in the private group, as cervical dystocia.

RETRODISPLACEMENTS OF THE POST-PARTUM UTERUS

SANFORD H. MOSES, M.D., BOSTON, MASS.

THE use of the knee-chest position for the prevention of retrodisplacement of the post-partum uterus is advocated by almost all writers on the subject. It had always appealed to me as a very rational and valuable procedure. In 1932, however, Schauffler[1] reported a series of cases in which it seemed to have had a deleterious effect. Forty-seven and two-tenths per cent of patients who had done the knee-chest exercises had retrodisplacement of the uterus when examined six weeks post partum while only 34.5 per cent of those who had not done the exercises had retrodisplaced uteri. More recently Eichner[2] found 22.7 per cent of retrodisplacements among patients who had done knee-chest exercises as contrasted with 27.7 per cent retrodisplacements among those who had not done the exercise.

A favorable opportunity to investigate the problem was provided at the Florence Crittenton Maternity Home, through the kindness of Dr. Thomas R. Goethals and the members of the staff of the hospital. The girls at the hospital remain there for at least six weeks after delivery. As they do their knee-chest exercises under supervision one may be sure the exercises were actually done and done correctly. (One of my patients once told me that I must have a beautiful faith in human nature if I thought that anyone actually did the exercises after she went home.) The statistics herein presented refer to a group of 210 girls who actually did the knee-chest exercises under supervision from ten days after delivery until their discharge examination six weeks post partum. A control series of 210 Crittenton patients

who did not do the knee-chest exercises were likewise examined six weeks post partum. The results are shown as follows:

TABLE I. PATIENTS WITH KNEE-CHEST POSITION

210 Cases Examined Six Weeks Post Partum for Retrodisplacements

	ANTERIOR	RETRODISPLACEMENTS				
		1ST DEG.	2ND DEG.	3RD DEG.	UNCLASSIFIED	TOTAL
No. of cases	136*	5	23	38	8	74
Per cent	64.7	2.4	10.9	17	3.8	35.2

*Includes 5 anteflexed, 5 good and 2 fair.

TABLE II. PATIENTS WITHOUT KNEE-CHEST POSITION

210 Cases Examined Six Weeks Post Partum for Retrodisplacements

	ANTERIOR	RETRODISPLACEMENTS			
		1ST DEG.	2ND DEG.	3RD DEG.	TOTAL
No. of cases	136	12	28	34	74
Per cent	64.7	5.7	13.3	16.1	35.2

The total number of retrodisplacements was exactly the same in both series. No significant variation appears in the degree of retrodisplacement. This seems to demonstrate that the knee-chest position is completely ineffectual in the prevention of retrodisplacement of the post-partum uterus.

I was unable to learn from what source the use of knee-chest position originally came. I suspect that it is one of those ideas handed down from generation to generation without ever being subjected to statistical study. It was used by Camper in the middle of the seventeenth century and by Deventer in 1701. Von Ritgen in 1820 also used it. The literature of sixty to seventy years ago is filled with debates on the mechanism by which it functions, the influence of air entering the vagina being stressed in several lengthy and highly technical papers. The knee-chest, knee-elbow and other variations of the posture are described. Apparently before the days of aseptic surgery, the knee-chest position was widely used in all types of retrodisplacements. I was unable to discover who first popularized its use in the puerperal state. That it is widely used for the prevention of post-partum retrodisplacements will, I think, be admitted by all, but statistical vindication of the practice seems to be entirely lacking.

A further check was provided by the study of 200 private cases. These patients were all instructed to assume the knee-chest position for ten minutes twice a day. The exercises were started ten days post partum. At the discharge examination from the hospital (usually

TABLE III. TWO HUNDRED PRIVATE PATIENTS SIX WEEKS POST PARTUM

	ANTERIOR	RETRODISPLACEMENTS			
		1ST DEG.	2ND DEG.	3RD DEG.	TOTAL
No. of cases	140	14	14	32	60
Per cent	70	7	7	16	30

fourteen days post partum) any retrodisplacements were corrected but no other treatment was given before the six weeks' examination.

There are 5 per cent less retroversions in this group than in the Crittenton series. The slightly better showing may not be at all significant. If the knee-chest position were effective, the series of Crittenton patients who did the exercises under supervision should show better results than these patients, many of whom were admittedly lax in their performance of the exercise at home. If any difference is shown it is probably due to the correction of retrodisplacements at the discharge examination fourteen days post partum and not to any difference in the method of using the knee-chest position.

An effort was made to determine the influence of parity on post-partum retrodisplacements. As all of the Crittenton patients were primiparas, 100 multiparas and 100 primiparas were chosen from my own cases. The results of their examination at six weeks and six months is tabulated below.

TABLE IV

	ANTERIOR	RETRODISPLACEMENTS			
		1ST DEG.	2ND DEG.	3RD DEG.	ALL RET.
One Hundred Private Primiparas					
6 Weeks	72	8	7	13	28%
6 Months	87	3	2	8	13%
One Hundred Private Multiparas					
6 Weeks	68	6	7	19	32%
6 Months	86	5	2	7	14%

Although no really significant difference appears, it would seem that multiparas are slightly more susceptible to post-partum retrodisplacement. One may surmise that this is due to the greater degree of relaxation found in multiparas. It is really surprising that a greater difference was not found.

It will be noticed that the six months' examination shows over a 50 per cent reduction in the number of retrodisplacements. This was obtained by the use of repeated replacements, pessaries and the knee-chest position. Contrary to the findings of Findlay[3] who reported that pessaries cured 75 per cent of retrodisplacements in primiparas and only 38 per cent in multiparas, the multiparas in this series seem equally amenable to treatment. All of the retrodisplacements at this time were apparently symptomless and were not treated further. Grouping the primiparas and multiparas, the following figures are obtained, showing the results at the end of six months.

TABLE V. TWO HUNDRED PRIVATE PATIENTS SIX MONTHS POST PARTUM

	ANTERIOR	RETRODISPLACEMENTS			
		1ST DEG.	2ND DEG.	3RD DEG.	TOTAL RETRO.
No. of cases	173	8	4	15	37
Per cent	86.5	4	2	7.5	13.5

This figure is well below the incidence to be expected in nulliparous women for both Polak[4] and Stacy,[5] independently and in large series of cases, have found that retrodisplacements occur in about 20 per cent of nulliparas. It is interesting to compare these figures with others gleaned from the literature.

TABLE VI. INCIDENCE OF RETRODISPLACEMENTS

AUTHOR	TIME POST PARTUM	NO. CASES	UNTREATED	TREATED
Beck[6]	-----	60	45.0%	
Beck[6]	-----	37	------	13.5%*
Danforth and Galloway[7]	8 wk.	1,000	------	14.4%†
Eichner[2]	6 wk.	191	27.7%	------
Eichner[2]	6 wk.	211	------	22.7%‡
Findlay[8]	-----	165	26.6%	------
Key[9]	13 wk.	100	33.0%	8.0%†
Litzenberg[10]	6 wk.	-----	25.0%	2.5%†
Lynch[11]	1 yr.	1,230	41.4%	------
Miller[12]	6 wk.	1,000	22.0%	------
Moses	6 wk.	210	35.2%	------
Moses	6 wk.	210	------	35.2%‡
Moses	6 wk.	200	------	30.0%‡
Moses	6 mo.	200	------	13.5%†
Polak[13]	-----	-----	35.0%	3.0%§
Schauffler[1]	6 wk.	84	34.5%	------
Schauffler[1]	6 wk.	84	------	47.2%‡

*Treated by monkey walk, and exercises on all fours.
†Treated by replacement and pessary.
‡Treated by knee-chest position.
§Treated by mule kick.

Although at first sight there may seem to be considerable variation in these series, by taking averages we can arrive at some reliable and confirmatory figures. There is a total of 3,040 untreated cases and the percentage of retrodisplacements figures out as 32.8 per cent. Two percentages are reported without giving the number of cases involved and these average 30 per cent.

The treated cases arrange themselves in three groups. Two authors speak of 3 per cent and 2.5 per cent retrodisplacements.

Dr. Polak's figures are taken from a discussion and Dr. Litzenberg's are obtained from his statement that 25 per cent of post-partum patients have retroversions and that 90 per cent of these may be corrected. Neither statement is supported by accurate figures and perhaps neither was intended to be taken as more than an estimate. Beck found 13.5 per cent retrodisplacements in his patients following monkey walk exercises and in two series replacement and pessary treatment left about 14 per cent of retrodisplacements. In the remainder, the knee-chest position used in a total of 705 cases gave a 32.2 per cent incidence of retrodisplacements, about the same as the incidence of retroversions in untreated cases. Comparison with the results of other forms of treatment serves to re-emphasize the futility of the knee-chest exercises.

From these figures, however, some very interesting conclusions may be drawn. The average percentage of retroversions found post partum in the absence of treatment is 32 per cent, well above the 20 per cent incidence in nulliparous women. Hence pregnancy results in a definite increase in the incidence of retrodisplacements of the uterus. The number of retrodisplacements persisting after treatment,

however, is from 3 to 14 per cent, definitely lower than the percentage of congenital retrodisplacements. Repeated replacement, pessaries, and perhaps exercise on all fours will afford the effective methods of treatment. The facts seem to demonstrate that the uterus is in a rather plastic state as involution progresses and that, by and large, it tends to remain in the position in which it is held while it is shrinking. Therefore unless adhesions are present, even congenital retrodisplacements may be corrected during the process of involution. While many retrodisplacements are symptomless, unless the cure is so difficult as to be worse than the disease, it is worth while to seize the opportunity of restoring the uterus to its normal position.

CONCLUSIONS

1. The knee-chest position is of no value in the prevention of post-partum retrodisplacements of the uterus.

2. Multiparas are little if any more prone to retrodisplacements of the post-partum uterus than primiparas.

3. Unless treatment is given, pregnancy increases the percentage of retrodisplacements found.

4. The plasticity of the pelvic organs, while the uterus is shrinking down after pregnancy, affords an opportunity for correcting retrodisplacements of the uterus including those of congenital origin.

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Folliculin determines the proliferation of epithelial glandular tissue but not the amount of milk secreted. If administered in large doses in the puerperium it inhibits milk secretion.

Corpus luteum and suprarenal cortex hormone do not have a direct or appreciable influence upon the mammary gland.

The thyroid gland although not of great importance is not entirely excluded from the mechanism of lactation. It works indirectly through the hypophysis.

Decidual extract definitely influences the secretory process of the mammary gland, but its action is only partial and probably reflexly acts on the hypophysis, because the mammary secretion is established when the decidua is expelled.

The anterior hypophysis determines proliferation and secretion of the mammary gland; it contains the hormone of lactation, prolactin. The test of Riddle is specific for the hormones of lactation.

MARIO A. CASTALLO

THE RETAINED CERVICAL STUMP*

With Special Reference to Nonmalignant Changes

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THE many discussions and the innumerable articles pertaining to the cervical stump revolve chiefly about the possibility of malignancy and about the value of total versus the subtotal hysterectomy, little attention being paid to the fate of the cervical stump that does not develop carcinoma. Gynecologists are prone to spend much time treating the many abnormalities of the cervix before the removal of the corpus, but to lose interest when only the stump remains, unless of course, evidence of malignant changes can be demonstrated. My attention was first drawn to the so-called normal cervical stump when a difference in the iodine absorption (Schiller's test) was noted before and following the removal of the corpus. Biopsy studies are naturally of little value in such cases because of the concomitant trauma to the neighboring tissue. It was possible to demonstrate a noticeable difference in the consistency of the vaginal portion of the cervix before and following the subtotal hysterectomy. The alteration in the vascularity of the retained cervices, together with the loss of the changes in diameter of the cervical canal which normally accompany menstruation, tend to stricture formation, with subsequent cervical pyometria. These strictures and abscesses are often overlooked in routine examination, especially when the portio vaginalis presents a grossly normal smooth surface and a small external os. Not infrequently it is this type of cervix that constitutes the causative source of backaches, urinary symptoms and a persistent leucorrheal discharge. Simple dilatation of the cervical canal usually results in quick relief.

During a recent clinical and pathologic survey of carcinoma of the cervix, occurring in the Gynecological Service of the Johns Hopkins Hospital between the years 1893 and 1935, I was impressed with the relative paucity of true stump carcinoma following subtotal hysterectomy. In this period of forty-two years, 4,300 uteri were removed subtotally because of myomas and 2,250 for other causes of a benign nature. In this series of 6,550 stumps, we have records of 157 patients returning because of complaints relative to the stump. Of the 157 patients, twenty-six were found to have primary carcinoma of the stump. This figure would be nearly tripled if we included those cases in which cancer was found either at the time of hysterectomy or within the period of one year following the surgery.

*Presented at a meeting of the Section of Gynecology and Obstetrics of the California State Medical Association, May, 1937.

Data from the Gynecological Department of the Johns Hopkins University.

There has been no definite attempt to follow these patients and the data for the most part have been taken from the case reports, so that our figures are relative rather than factual. Many of the statistical reports giving the incidence of stump cancer have been obtained by

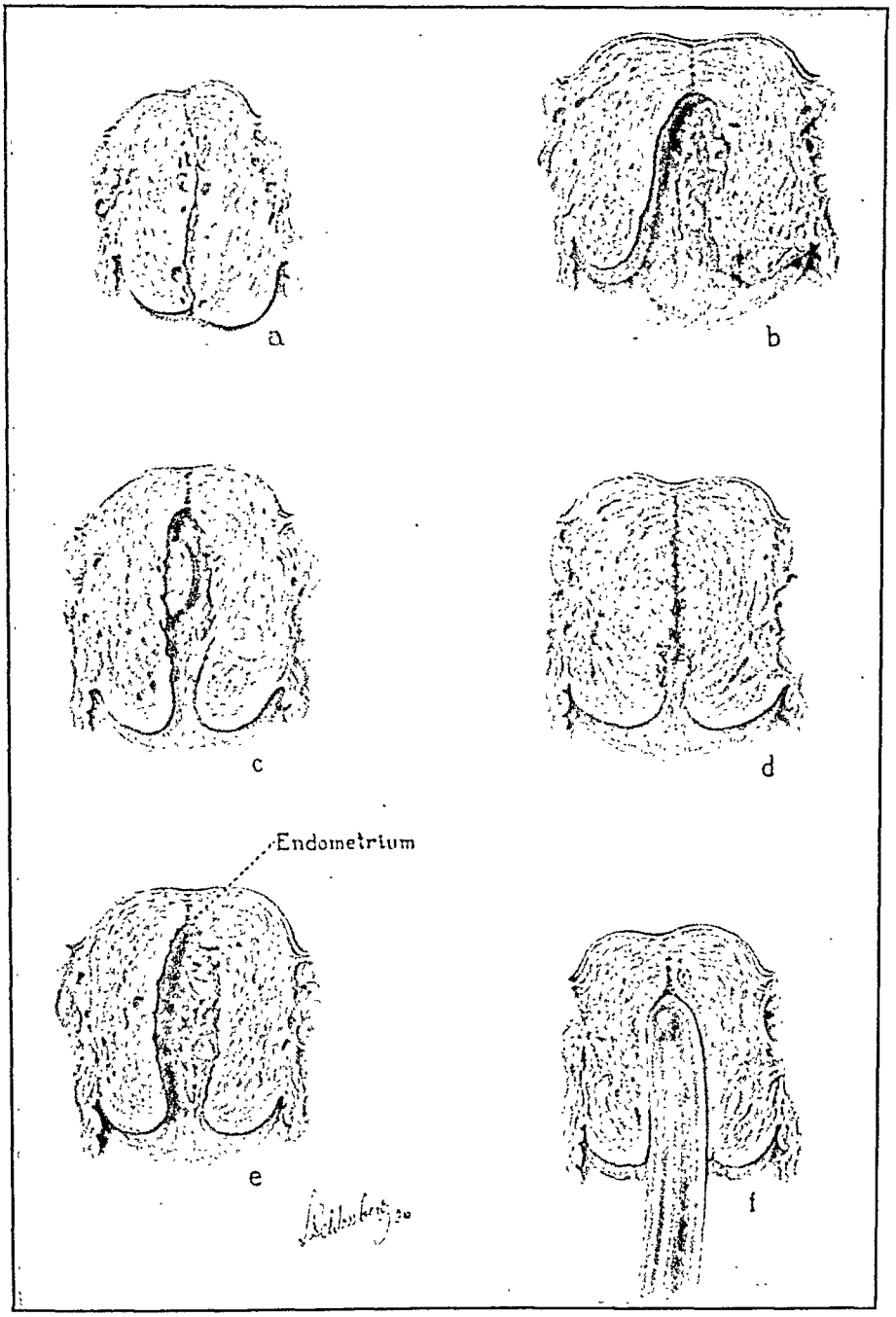


Fig. 1.—*a*, Cervical stump eight years after subtotal hysterectomy showing stricture of the external os with abscess formation in the walls of the canal. *b*, Large hypertrophic cervical stump with so-called erosion of the mucosal elements; there is also a marked inflammatory process. *c*, Two cervical polyps; the one near the os is polypoid in type while the larger growth is flat with a wide base. The cyst on the cut surface is a dilated infected cervical gland. *d*, Cervical stump nine years after subtotal hysterectomy, showing a relatively early intracervical carcinoma of squamous-cell type. *e*, Cervical stump with small islands of functioning endometrium at the apex of the canal. *f*, A No. 9 Hegar dilator introduced into the stump pictured in *a*; providing adequate drainage will frequently clear up these abscesses.

studying series of cases of cervical cancer; this certainly does not express the true incidence. Thus, instead of the 2 to 5 per cent usually cited, our apparent incidence of cervical stump cancer is 0.45 per cent.

While we cannot belittle the importance of the possible later appearance of malignancy in the retained stump, we do feel that the "forgotten stump," the stump that does not show malignant changes, should receive more of our attention. In this series of 6,550 cases, 131 women presented themselves and were admitted to the service because of symptoms arising from benign changes in the cervical stump. Obviously we can give no figures of the many women following subtotal hysterectomy who might have suffered from symptoms referable to a diseased stump and who did not present themselves for assistance.

The following lists the primary complaints impelling patients in this series to seek medical assistance:

	BENIGN	WITH CANCER
Periodic vaginal bleeding	75	1
Irregular vaginal bleeding	22	7
Vaginal discharge, odorless	32	3
Vaginal discharge, offensive odor	19	6
Vaginal discharge, with bleeding	20	9
Prolapsus of the stump	3	0
Urinary symptoms	4	0
	157	26

Periodic Vaginal Bleeding.—The common cause of periodic vaginal bleeding following subtotal hysterectomy is high amputation of the corpus, and the bleeding is therefore an indication of menstrual activity. Most of these patients returned because they had been told they would not menstruate following the operation. The bleeding was always scant and rarely lasted for more than a day. In each instance dilatation and curettage of the cervical canal was done, and in 52 of the cases evidence of retained functional endometrium was demonstrated. It is therefore important that patients with this type of bleeding be carefully instructed as to further possibilities, especially as regards menstrual cycle changes. Four of the 57 cases were found to have an associated endometriosis of the portio vaginalis of the cervix and were treated with the actual cautery. One patient returning twenty-two months following the operation was found to have an adenocarcinoma of the stump. Careful reexamination of the removed corpus failed to disclose any evidence of malignancy that had been overlooked previously. This patient stated that she had experienced a regular scant period each month following the removal of the corpus. She returned because her periods had become increasingly profuse for the past three months.

Irregular Vaginal Bleeding.—Of the 22 patients presenting this complaint, seven had definite malignancy of the stump. We feel that this is the most dangerous group in the series. Patients are not infrequently advised not to be alarmed if they experience scant bleeding on several occasions following the subtotal hysterectomy. Naturally, the patient is likely to interpret such bleeding when it does occur as of no importance. Again, not infrequently abnormal bleeding may even appear several years following the operation and may then be considered as an indication of the menopause. The patients in this group in whom benign lesions were found, presented for the most part, functioning endometrium in association with chronic infections of the cervix or cervical polyps and were treated by cervical cauterization.

Odorless Vaginal Discharge.—Of the 32 patients complaining of an inoffensive vaginal discharge, varying in amount from a self-termed "moderate" to "profuse,"

3 had cancer of the stump. During the past five years, 2 patients who have been examined showed the presence of *Trichomonas vaginalis* infection and responded to specific therapy seemingly more readily than those patients in whom there was a normal menstrual cycle. Twelve of the series were relieved by simple dilatation of the canal and in 8 of these patients retained secretion above the stricture of the external os was demonstrated; the remaining 15 patients were cauterized following the routine dilatation and curettage of the canal.

Offensive Vaginal Discharge.—In this group, 6 of the 19 patients presenting a foul discharge and no evidence of bleeding were found to have cancer. Most of them returned to the hospital complaining of the foul odor and not because of the discharge per se. Four were found to have endocervical polyps, and in 2 patients, definite stricture of the external os with abscess formation was demonstrated.

Vaginal Discharge With Spotting.—There were 20 patients complaining of vaginal discharge with various degrees of bleeding; 9 of these had cancer of the cervical stump. One had endometriosis of the posterior vaginal fornix and an associated marked cervicitis. Cervical polyps were present in two instances, and a small endometrial polyp was demonstrated in one patient. In the cases showing malignant changes in the cervical stump, the average time elapsing between the onset of the bleeding and the patient's appearance for aid was six months; this corresponds closely with the period of delay in cervical carcinoma cases in general.

Prolapsus of the Stump.—We have records of three such instances. Oddly enough 2 of these patients were in their early twenties, the uteri having been removed for lesions other than myomatous involvement. In each instance the stump was suspended by ventroabdominal fixation.

Urinary Symptoms.—Though urinary complaints are not uncommon following either the total or subtotal operation, only 4 patients presented themselves with symptoms of urinary tract irritation that were not alleviated by urinary tract antiseptics, cystoscopy, or topical applications of drugs to the urethra and trigone. In each instance, there was evidence of upper urinary tract irritation with negative bladder cultures. Though topical applications of drugs and bladder instillations gave temporary relief, it was not until the badly infected cervices were properly treated by the cautery that the urinary symptoms were permanently relieved.

The routine instructions to all the public ward patients at the Johns Hopkins Hospital following any type of operation is to return to the outpatient department at the end of six weeks and again at the end of the first year. At each examination careful note is made of the cervix. If, when examined in the outpatient department, the history or the examination suggests any unusual change in the cervical stump, the patient is admitted to the wards. The cervix is well exposed and the canal is dilated and curetted. If the gross appearance of the obtained tissue does not suggest malignant change, the cervix is then cauterized. If the pathologic report shows malignancy, radiation is immediately instituted. The most frequent pathologic finding is chronic inflammatory tissue and "metaplastic" epithelial changes are not infrequent. Though no statistics are available it is my impression that metaplasia or epidermidization is more frequent in cervical stumps than in other cervices. Many of these patients who complain of leucorrheal discharge in the absence of cancer show definite evidence of stricture about the external os, in spite of the presence of deep lacerations. We have treated these strictures by dilating the canal to the size of a No. 12 Hegar dilator, generally this is more efficacious than the cautery, but care must be taken not to tear the cervix during the insertion of the dilators. Another adjunct in the examination of the

residual cervical stump, especially in office practice, is the suction curette; this is easily inserted into the canal and, if endocervical malignancy is present, tissue is more readily obtained than follows the use of the usual biopsy forceps.

No article on the cervical stump would be complete without at least some comment upon the problem of the relative advantages of subtotal versus total hysterectomy, as a routine procedure. Our comment, or rather our plea, is directed to the occasional operator rather than to the trained specialist. The time is past when surgery is confined to medical centers with highly trained staffs. We feel that the authors who have and are still debating the value of the two operations have missed the point. It is possible that in the hands of the highly trained specialist there is little difference in the morbidity and mortality rates of the two operations, but in the hands of the less expert surgeon with his operating staff of untrained assistants, the rates do vary to a marked degree. The man in the small community derives his ideas of advancement in technique from the publications of expert gynecologists and with his limited facilities has little opportunity to prove or disprove what he reads. To use the now common term, he is the "forgotten man," and it is for his benefit and to suit his circumstances that suggestions should be made more frequently than they are.

The fact that only 2.4 per cent (157 patients) of our 6,550 patients returned to the hospital with complications referable to the stump, and that of these, we have records of only 26 or a percentage of 0.45 showing cancer, indicates that the incidence of stump cancer is so low as to be of relatively little import. There is no evidence that subtotal hysterectomy predisposes to cancer of the stump or that the residual stump is more susceptible to malignant changes than the cervix of a complete uterus. We do not feel that the 0.45 per cent incidence of stump cancer is sufficient reason to advise the total operation with its morbidity-mortality rate of 2 to 5 per cent. It is common knowledge that in the hands of the less experienced surgeon, total hysterectomy is accompanied with greater risk than when the more conservative operation is employed. The more rational approach would be to fit the operation to the patient and to the physical findings, rather than to advocate either operation as a routine. In considering the choice of operation, one must take into account the surgical ability of the operator and the condition of the patient as well as the possibility of later development of cancer of the stump. With proper pre- and postoperative treatment of the cervix, total hysterectomy merely as a prophylactic against cancer of the stump is probably rarely indicated.

SUMMARY

1. An endeavor has been made to show that the incidence of cancer of the cervical stump is exceedingly low, when studied from the standpoint of its occurrence in a series of subtotal hysterectomy cases, rather than its occurrence in a series of cases of cervical cancer alone.

2. We have the records of 157 patients out of 6,550 subtotal hysterectomy cases presenting themselves with symptoms referable to the stump and have classified them according to their complaints.

3. In the hands of those who are not expert in pelvic surgery, total hysterectomy is a more dangerous procedure than the more conservative subtotal operation. The exceedingly low incidence of stump cancer is not sufficient reason to advocate the routine use of the total operation. The ideal procedure in most cases consists of proper conservative care of the cervix before removing the corpus, followed by periodic examinations of the stump after operation.

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THE EFFECT OF PROGESTIN UPON THE ANTERIOR PITUITARY

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IT IS undesirable and dangerous to draw inferences from the results of experimental work in one species and to expect these inferences to hold true in detail in another. Basic physiologic principles, however, usually carry over from species to species, in a modified form at least.

Progestin, one of the ovarian hormones secreted by the corpus luteum, exerts an effect upon two components of the uterus, the muscle and the endometrium. The endometrium is changed from the proliferative stage to the secretory or progestational type in both the rabbit[1] and the human being.[2] The hormone inhibits the normal response of the uterine muscle of the rabbit to extracts of the posterior pituitary.[3, 4] Similar action in the human being is reported,[5-7] although other investigators cannot confirm the finding.[8-10] Thus we see that the action of progestin upon the endometrium in both rabbit and man is similar, as is possibly also its action upon the uterine muscle.

It has been known for many years that rabbits in heat will mate and ovulate ten to twelve hours later.[11] It has also been common knowledge that rabbits mate during pregnancy and pseudopregnancy, but never ovulate following these matings.[11] During pregnancy and pseudopregnancy there are present in the ovary functional corpora lutea, and it was generally acknowledged that these glands probably played a part in suppressing ovulation; the mechanism of the action remained, however, obscure.

Pseudopregnancy might be described at this time for those unfamiliar with the reproductive mechanism in the rabbit. Rabbits ovulate only after sexual stimulation of some sort, the natural and commonest one being copulation. A doe mated with

a vasectomized buck ovulates, corpora lutea form, but since there are no sperm in the female generative tract, the ova are not fertilized. The corpora lutea so formed are functional and normally do not begin to degenerate until the fifteenth or sixteenth day after mating. This sixteen-day period is generally termed pseudopregnancy.

In attempting to demonstrate the active factor responsible for this suppression of ovulation in the rabbit, it was first shown that a change in sensitivity of the ovarian follicle to gonadotropic material was not the reason for the failure. On the eighth day of pseudopregnancy, only one-third more gonadotropic material was necessary to cause ovulation than was the required dose for a rabbit in heat.[12] The pituitaries of these eight-day pseudopregnant animals were known to contain many times more activity than was represented by the minimal effective dose administered.[13] The conclusion was reached, therefore, first that the follicles could and would ovulate if essentially normal amounts of gonadotropic material were released to the blood stream and second, that ample material to cause ovulation was contained in the anterior pituitary gland.

Interest was next directed toward the hormonal status of the anterior pituitary of the rabbit during pseudopregnancy, both before and after coitus.

The gonadotropic content of the pituitary gland on the eighth day of pseudopregnancy was examined both before and after coitus in order to determine the effect, upon the pituitary, of copulation during the active life of the corpora lutea. As controls, pituitaries of estrous (post partum) rabbits were taken and also of rabbits twenty-four hours after a mating which had been shown to have resulted in ovulation. The results in summary form are as follows: The gonadotropic content of the estrous glands was approximately 25 Rb. U. Twenty-four hours after a mating which resulted in ovulation, the pituitary contained 5 Rb. U. or less. Therefore, normally in estrous animals as a result of the stimulus of coitus, there is a nearly complete discharge of the gland. At the eighth day of pseudopregnancy, the gonadotropic content of the pituitary has been restored to at least the estrous level.[13, 14] However, when these pseudopregnant rabbits accept the buck and their pituitaries are removed twenty-four hours later, it is found that there has been insufficient discharge of gonadotropic material to be detected.[15] Consequently, during pseudopregnancy and presumably pregnancy, ovulation does not occur because the normal discharge of gonadotropic material from the pituitary following coitus is in some way inhibited.

The next step in the problem was to investigate the effect of progestin upon the pituitary. Progestin in doses of 2 Rb. U. or progesterone, the pure crystalline hormone, in doses of 2 mg. given daily for five days to estrous rabbits was found to inhibit ovulation normally following coitus.[16] No rabbit, after taking the buck, ever ovulated when receiving this or a larger dose. When the pituitaries of these mated animals receiving corpus luteum hormone were compared, as to gonadotropic content, to those of identically treated un-

mated animals taken as controls, it was found that there had been no detectable discharge of gonadotropic material from the glands.[17]

These results seem conclusive and permit one to state that pregnant and pseudopregnant rabbits do not ovulate because functional corpora lutea in their ovaries, by secreting progestin, prevent discharge of the gonadotropic content of the pituitary. Neither the mode nor yet the site of action of the hormone is explained by these results. It could conceivably act in any of several ways; one, by preventing the stimulus of coitus from reaching the pituitary or two, by preventing the discharge of the material into the blood stream, presuming the stimulus to have arrived, or three, by still some other action of which we have at present no clue. Experiments to demonstrate these unknown factors will have to be devised and carried out and also additional experiments planned to show whether or not one is correct in anticipating that progestin, in the human being, will be found to have a definite action upon the anterior pituitary gland similar in general to that which has been demonstrated to be true in the rabbit.

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Rorke, Margaret: Gonorrhea in Women and Children, Lancet 1: 932, 1938.

The author reviews the signs and symptoms of gonorrhea in women and children. The frequency of rectal infection is noted, and the necessity of rectal examination during the treatment of every case is emphasized.

Treatment advised by the author consists of rest, douches in the presence of profuse discharge, topical applications and the administration of prontosil album in 3.5 to 4 gm. daily doses for seven days, if tolerated, followed by one-half this amount daily for another week. The use of heat therapy with the Elliott machine is recommended in pelvic infection.

In the child local cleanliness, with either estrogenic hormone therapy or prontosil album in 1 or 2 gm. daily doses (given in 4 divided doses), is advised.

The test of cure is described as negative films and cultures immediately following three menstrual periods, the last at least after a month without treatment and following provocative painting of the cervix or alcohol stimulation. The importance of routine cultures is emphasized, as in 323 out of 871 cases studied the films were negative and cultures positive.

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FOOD HABITS OF MOTHERS OF CONGENITALLY MALFORMED CHILDREN

Report of 545 Families

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CERTAIN characteristics of a series of families, each of which had given rise to a congenitally malformed child, were the object of a recent investigation.[1-12] The study was planned to determine if any characteristic of these families might have predisposed to the occurrence of the malformations in the offspring. Advanced parental age was found to be such a predisposing factor, because the older couples gave rise to malformed children more often than did the younger ones.[6]

The food habits of the mothers likewise were studied with the same idea in mind, an analysis of the data upon this point forming the basis for the present report.

The essential components of an adequate diet during pregnancy indicate that minerals and vitamins should be increased at this time to supply the extra demands made upon the mother by the fetus (Table I). To accomplish this, in terms of foods, the following changes are usually made from the normal diet:

BASIC FOODS FOR THE NORMAL DIET OF ADULT WOMEN USE DAILY	BASIC FOODS FOR THE DIET DURING PREGNANCY USE DAILY
1 pint milk	1 quart milk
1 to 2 servings leafy vegetables	2 to 3 servings leafy vegetables
2 to 3 servings other vegetables	2 to 3 servings other vegetables
1 to 2 servings fruit	3 to 4 servings fruit (1 or 2 servings citrus fruit)
3 slices bread	3 or more slices bread, *whole grain varieties* preferred
1 serving meat or fish	Meat or fish as recommended by physician
1 egg	1 egg
1 to 2 ounces of butter	1 to 2 ounces of butter
Vitamin concentrates as directed by physician	Cod liver oil or vitamin A, B_1, and D concentrates as directed by physician

MATERIALS AND METHODS

Collection of Data.—There were located in the files of the Bureau of Vital Statistics, Department of Health of the State of Pennsylvania, 130,132 death certificates for stillborn and liveborn individuals who died in Philadelphia during the five years between Jan. 1, 1929, and Dec. 31, 1933. Each of these certificates was examined and among them were found 1,476 cases of congenital defect.

The deceased individual was considered to have possessed an abnormality under either of two conditions: (1) if the malformation involved the surface of the body, or (2) if internal, its presence had been disclosed by operation or necropsy. Diagnoses not conforming to these requirements were considered as not verified and were excluded from further consideration. This procedure gave 890 cases for study.

TABLE I. COMPARISON OF DAILY FOOD REQUIREMENTS* FOR THE NONPREGNANT AND PREGNANT WOMAN

DAILY ESSENTIAL	NONPREGNANT WOMAN	PREGNANT WOMAN
Calories	2,000 to 2,600	2,000 to 2,600 for first 3 months 2,400 to 3,000 for second 3 months Decrease to 2,000 to 2,200 during last 2 months if gain in weight is more than normal
Protein	1 gm. per kilo	1 gm. per kilo during first 3 months 1.5 gm. per kilo during later months
Calcium	0.55 to 0.68 gm. (0.023 gm. per 100 calories)	1.0 to 2.0 gm.
Phosphorus	1.06 to 1.32 gm. (0.044 gm. per 100 calories)	1.5 to 2.0 gm.
Iron	15 mg.	18 to 20 mg.
†Vitamin A	6,000 international units, at least	An increase desirable
†Vitamin B_1	300 international units	An increase desirable
†Vitamin C	300 international units	An increase desirable
†Vitamin D	400 international units	An increase desirable
†Vitamin G	400 to 600 Sherman-Bourquin units (20 units per 100 calories)	An increase desirable

*See references 13-15.
†See reference 16.

TABLE II. DIAGNOSES OF CHIEF CONGENITAL MALFORMATIONS BY SYSTEM

Showing the distribution of the congenital defects in the offspring of the mothers who answered the food questionnaires, arranged by body system. Each individual is represented by his most serious defect in cases in which two or more malformations were present.

SYSTEM	INDIVIDUALS
Central nervous	383
Gastrointestinal	72
Cardiovascular	51
Skeletal	32
Genitourinary	3
Multiple	3
Respiratory	1
Total	545

The malformed offspring are grouped in Table II according to the diagnosis of the chief defect. The serious nature of the defects is indicated by the fact that approximately 90 per cent of the malformed children were either stillborn or died within a year of birth.

An attempt was made to interview the mother of each defective individual, the visits being carried out in the summer of 1934 by four fourth-year medical students. Each visitor was supplied with a five-page questionnaire, one sheet of which contained the following questions bearing on diet:

1. How much milk do you use daily in any way?
 None 1 cup 2 cups 3 cups 4 cups
2. What green vegetables do you like and eat? How often? Once or twice daily? Once or twice weekly?
3. What other vegetables do you like and eat? How often?
4. What fruit do you like and eat? How often?

5. How much bread do you generally eat? _____ slices per meal. What kind of bread?
6. What foods do you like and eat most often?
7. How much coffee do you generally drink? _____ cups.
 How much tea do you generally drink? _____cups.
 How much beer, wine or other such drinks do you take daily? _____ glasses.
8. Did you eat about like this when you were pregnant? Yes _____ No _____
 Differences:

RESULTS

Examination of the answers to the food questions revealed considerable variation in the skill and accuracy of recording. After eliminating the questionnaires which were not filled out satisfactorily, 545 were considered suitable for analysis.

FOOD DATA

Milk.—Facts upon the use of milk appear in Table III. Of the 526 women who reported, 40 per cent used none, and of the 60 per cent who used milk, 45 per cent used less than one quart a day.

TABLE III. DAILY CONSUMPTION OF MILK

Showing the usual daily consumption of milk by the mothers of the malformed children. Note the high percentage of mothers (40 per cent) who took no milk.

MILK	MOTHERS	
	NUMBER	PER CENT
None	208	40
Less than 1 quart	241	45
1 quart	72	14
Over 1 quart	5	1
Total	526	100

More women reported increased use of milk than of any other single food. Twenty-four (4.5 per cent), who did not use milk regularly in their diet, reported using more during pregnancy. Thirty-one women (6 per cent) took from 1 pint to 1 quart more milk when pregnant.

Adjusting these figures to those obtained on the regular use of milk, the significant facts about its consumption by this group are: About 35 per cent took no milk during pregnancy, and about 20 per cent took 1 quart or more daily.

In this country, one quart of milk daily is the usual recommendation for the normal expectant mother. It is recognized as the most valuable single food source of calcium and phosphorus in good amounts and good proportions during pregnancy. American mothers who habitually take less than one quart daily are usually on calcium and phosphorus deficient diets. Using a standard of one quart of milk daily, 80 per cent of these mothers were on diets low or deficient in these minerals.

Vegetables.—The use of vegetables was reported upon by 518 women (Tables IV and V). Only 19 women (4 per cent) reported eating more vegetables during

TABLE IV. LEAFY VEGETABLES

Showing the use of leafy vegetables by the mothers of the malformed children. Note the small percentage of mothers who used two or more servings of leafy vegetables daily.

SERVINGS	MOTHERS	
	NUMBER	PER CENT
1 weekly	23	4
2 weekly	89	17
3 or 4 weekly	29	6
1 daily	290	56
2 daily	89	17
3 daily	6	1
Total	518	100

TABLE V. NONLEAFY VEGETABLES

SERVINGS	MOTHERS	
	NUMBER	PER CENT
Less than 1 daily	52	13
1 daily	236	58
2 daily	93	23
3 or 4 daily	24	6
Total	405	100

pregnancy, so the above figures are fairly representative of the amount of vegetables consumed. If two servings of leafy vegetables and two to four servings of other vegetables daily be accepted as a desirable amount during pregnancy, allowing for 4 per cent increased consumption of both kinds of vegetables, only 20 per cent of the mothers ate adequate amounts of leafy vegetables, and only about 10 per cent consumed desirable amounts of the other vegetables.

As vegetables in general, and leafy vegetables in particular, are valuable sources of calcium, phosphorus, iron, roughage, vitamins A and G and also for C, if eaten raw, low amounts in the diet tend to contribute to mineral and vitamin deficiencies.

Fruit.—The use of fruit was reported upon by 467 women (Tables VI and VII).

TABLE VI. FRUIT

SERVINGS	MOTHERS	
	NUMBER	PER CENT
None (or only occasionally)	58	12
Less than 1 daily	94	20
1 daily	255	54
2 daily	43	10
More than 2 daily	17	4
Total	467	100

TABLE VII. CITRUS FRUIT

SERVINGS	MOTHERS	
	NUMBER	PER CENT
None	14	6
Less than 1 daily	122	55
1 daily	74	33
2 daily	13	6
Total	223	100

Thirteen women (2 per cent) reported eating more citrus fruit during pregnancy and 17 women (3 per cent) said they ate more fruits in general. Adding this increase to the figures on the usual intake of fruit, about 18 per cent had citrus fruit once daily and 13 per cent had about two servings of other fruit daily.

Citrus fruit is of special value in the prenatal period for increasing vitamin C in the diet. Its regular use, one to two servings daily, is highly desirable. Citrus as well as other fruits also make valuable contributions to the mineral, vitamin, and laxative properties of the diet. Less than one-fourth of this group reported eating the amounts of fruit usually recommended to expectant mothers.

Bread.—The use of bread was described by 520 women (Table VIII). Five mothers (1 per cent) reported eating less bread, and 5 reported eating more during pregnancy.

The usual suggestion about the use of bread during pregnancy is about two slices per meal. Larger amounts tend to replace the more valuable fruits and vegetables. About 57 per cent of this group reported two slices or less per meal. Approximately 25 per cent used too much bread.

Whole grain breads contain approximately 50 per cent more minerals than white bread, and are a valuable source of vitamin B_1. Their use during reproduction makes a definite contribution to the mineral and vitamin B_1 adequacy of the dietary. Only 17 per cent used whole grain bread regularly or often.

TABLE VIII. BREAD

BREAD	MOTHERS	
SLICES PER MEAL	NUMBER	PER CENT
None or less than 1	47	9
One	94	18
Two	158	30
Three	92	18
Four	71	14
Five	30	6
Six	8	1
More than 6	20	4
Total	520	100

Kind of Food Liked and Eaten Most Often.—This question was asked as a possible means of better understanding food habits and as a check on the other food facts given. The answers are summarized in Table IX. The food preferences as listed

TABLE IX. FOODS EATEN MOST OFTEN AND MOST DESIRED

KIND OF FOOD	NUMBER OF WOMEN
Vegetables	163
Meat	152
Potatoes	146
Cereals	54
Eggs	33
Fruit	23
Fish	17
Soups	15
Bread	9
Sweets	8
Cheese	2

seemed to confirm other dietary facts and include foods which should contribute to a good diet if used in adequate amounts. Economic conditions are a definite factor in determining the type of food eaten most often, for many women listed these foods with the phrase "if I can get it."

Coffee, Tea, and Alcoholic Beverages.—The data on the consumption of coffee, tea, and alcoholic beverages showed no abnormal or excessive use of any of these beverages.

Changes Made in Diet During Pregnancy.—The changes made in the diet during pregnancy are summarized in Table X.

TABLE X. CHANGES MADE IN DIET DURING PREGNANCY

	MOTHERS	
	NUMBER	PER CENT
Mothers reporting	526	100.0
No change in diet	346	65.8
Ate more	24	4.5
Ate less	34	6.4
Drank more milk	24	4.5
1 pt. to 1 qt. more of milk	31	6.0
More vegetables	19	—
More oranges	13	—
Other fruit	17	—
Less meat	12	—
Less bread	5	—
Less vegetables	5	—
More candy	4	—
More condiments	4	—
More potatoes	2	—
More eggs	1	—

Adequacy of Diet.—The present figures show that the protective foods, such as milk, leafy vegetables, fruits, and whole grain breads were present in the diet of these women in amounts too low to meet the mineral and vitamin standards as recommended for expectant mothers, no one of which reported the use of any vitamin concentrate. The most obvious dietary deficiencies were in calcium, phosphorus, iron, vitamins B_1, C, and D. As each of these essentials is important for physiologic well-being, especially during pregnancy, the diet of this group of women was obviously far below desirable standards.

Anemia.—Estimations of the hemoglobin made when the patients were pregnant with their malformed offspring were available for 90 (16 per cent) of the 545 mothers. Of these 90 women, 41 (45 per cent) gave hemoglobin estimations of less than 70 per cent of normal. Reid and Mackintosh[17] in a study of 1,000 pregnant women, found only 10 per cent with a similar degree of anemia. Therefore, the mothers of the malformed children presented a frequency of anemia which was four times that found in the series reported by Reid and Mackintosh.

Of the 90 women for whom hemoglobin estimations were available, 37 (41.2 per cent) used an inadequate diet. Of the latter, 23 (62.2 per cent) had hemoglobin estimations of less than 70 per cent of normal. Whereas, of the 53 who used a balanced diet, only 18 (34 per cent) showed an equal degree of anemia. Therefore, anemia was found in association with an inadequate diet nearly twice as frequently as with an adequate one.

No data were available upon the hemoglobin content of the blood of the malformed offspring.

The present report offers no proof that the inadequate diet of the mothers or the associated anemia were predisposing causes to the occurrence of the congenital malformation in their offspring. It would seem to be within the realm of possibility, however, that dietary deficiency might be a predisposing factor.

SUMMARY AND CONCLUSIONS

An attempt was made to obtain dietary facts from mothers who had given birth to children with congenital defects. Accurate quantitative food intake data could not be secured, but efforts were directed toward obtaining facts about the quality and the possible adequacy of the diet. On the basis of generally accepted dietary suggestions for expectant mothers, questions were planned which might be the means of assembling information about the regular food habits of this group of mothers and the changes they made in their diet during pregnancy.

Records from 545 women were studied. An analysis of the dietary data which they gave to the medical examiners showed:

1. About 35 per cent of this group of women took no milk during pregnancy.
2. About 20 per cent took one quart or more daily.
3. About 20 per cent had two servings daily of leafy vegetables and only 10 per cent reported having 2 to 4 servings daily of other vegetables.
4. Eighteen per cent reported using citrus fruit once daily and 13 per cent had about two servings of other fruit daily.
5. About 25 per cent used too much bread and only 17 per cent used whole grain bread regularly or often.
6. Excessive use of coffee, tea, or alcoholic beverages was not indicated by the reports given.
7. Approximately 40 per cent of these women had an inadequate diet when pregnant with their malformed offspring.
8. Among the mothers using an inadequate diet, anemia was found twice as frequently as among those using an adequate diet.

9. Anemia in the women who gave birth to congenitally malformed children was found four times as often as in a control series.

10. The present observations offer no proof that an inadequate diet or anemia are predisposing causes for the occurrence of congenital malformations. It is of interest, however, that both characteristics should have been observed with unusual frequency.

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ANTE-PARTUM RUPTURE OF THE UTERINE SCAR FOLLOWING LOW FLAP CESAREAN SECTION*

With a Report of a Case Giving Rise to a Secondary Abdominal Pregnancy

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THE rupture of a low flap cesarean section scar during a subsequent pregnancy has been reported but infrequently. The subject has not received the attention accorded the same type of accident following classical cesarean sections. It is my purpose to review the subject, and to add a case of such rupture, which is extremely rare as to causation and end result.

For the sake of comparison, some of the historical aspects of uterine rupture following the classical type of cesarean section will be briefly reviewed.

Krukenberg,[1] in 1886, reported 20 cases of rupture of the uterus during pregnancy in patients having had classical cesarean section, and stated that one-half of all cesarean scars ruptured during a subsequent pregnancy, with a 50 per cent mortality in the patients suffering the accident. According to Porro[2] it was the custom at that time to return the unsutured uterus to the abdominal cavity, with little or no attempt to control hemorrhage. It is not surprising, therefore, to find that Harris,[3] in 1878, reported that of 80 cesarean sections done in the United States up to that time, 52.5 per cent of the patients died following the operation. If the figures of Krukenberg and Harris are combined, it becomes apparent that of 100 women having cesarean section at that time, 47 would survive. If these 47 again became pregnant, 24 would have a rupture of their uterus and 12 would die. If it became necessary for the surviving 36 to have a second cesarean section, only 18 of the original 100 patients would survive. This was sixty years ago.

A few years later, in 1882, Sänger[4] wrote his classical monograph on the proper method of suturing the incised uterus. This was a turning point, for in the following thirteen years he observed 500 consecutive patients who had gone through

*Presented at a meeting of the New York Obstetrical Society, May 10, 1938.

pregnancy following cesarean section without a single case of ruptured uterus. This would be unusual even today, so it might be well to note the fact that he used linen suture material throughout the uterine incision.

Palmer Findley,[5] in 1916, reviewed the literature from the time of Krukenberg, and found reports of 63 cases of rupture of the pregnant uterus subsequent to a cesarean section. Asa B. Davis,[6] in 1927, reported 24. La Mariana,[7] in 1933, brought the total number of cases to 175. We have found 36 others since that time, making a total of 208. Casual conversation in any obstetric group, however, will convince one that this is probably only a small portion of the cases, as many men do not bother to report such a common complication. The percentage of uterine ruptures following classical sections varies from 2 per cent according to Kerr,[8] to 6 per cent according to Audebert,[9] but the generally accepted figure seems to be 4 per cent. Holland[10] has further found that 43 per cent of such ruptures take place before the onset of labor, while 57 per cent occur during labor. The estimated mortality varies from 13 per cent according to Asa B. Davis, to 50 per cent according to Weber.[11] Our review of several other series indicates a general mortality of about 30 per cent, the rate apparently depending on the availability of hospital facilities.

The statistical background of the cervical or low flap cesarean section presents a slightly different picture. The operation originated after the advent of aseptic surgery, and has been essentially a procedure to be carried out only by the experienced obstetrician. The results have been colored, therefore, by the absence of many of the catastrophes resulting from casual abdominal surgery. The operation as we know it today originated about 1907, and has since undergone numerous modifications.

Wettenwald,[12] in 1926, reviewed 3,600 pregnancies in patients who had a previous low flap cesarean section. Gellé,[13] in 1932, again reviewed all available cases. Both observers reported that the incidence of rupture of a pregnancy subsequent to this type of procedure was about 0.25 per cent, or 1/16 of that found following the classical type of operation. A painstaking review of several thousand low flap cesarean operations reported since that time have confirmed these findings. The total recorded number of cases of ruptured uterus following low flap cesarean section to date is 36. Of these, only 3 have occurred before the onset of labor. This is less than one-fifth the number rupturing ante partum in the classical cesarean section series. The mortality following rupture is about the same in both types of operations.

In studying these cases of ruptured uterus following the low flap cesarean section, a few predisposing factors seem to stand out. (1) Local infection at the time of previous section, as manifested by foul lochia and a febrile postoperative course, (2) hurried closure of the uterine wound due to the patient's condition, (3) low implantation of the placenta on the uterine wall, over the scar of the previous section.

This latter is the most important and most constant factor, for it was found repeatedly in the cases reviewed. It is reasonable to assume that this is also the explanation of those cases in which a patient delivers spontaneously following a cesarean section and then suffers a ruptured uterus in the third pregnancy. It is being stressed, too, because of its presumptive importance in the case to be reported.

There is another frequent observation which should be emphasized, namely, that in those patients in which the product of conception was completely expelled from the uterus through the site of rupture, hemorrhage was moderate and recovery the rule. Partial expulsion, on the other hand, prevents uterine contraction and may be the direct cause of a fatal hemorrhage. Cameron[14] seems to have been the first to stress the importance of this point.

Practically every case studied brought out the point that rupture of these low flap scars was "silent," or practically symptomless, the accident being discovered only at the time of operation.

Of the three previously reported cases of ante-partum rupture following low flap cesarean section, the most interesting was that of Perez and Talioferro.[15] Briefly, this patient had a separation of the uterine scar early in a pregnancy which followed a low flap cesarean section for placenta previa. A second low flap cesarean section

was performed in the eighth month of gestation, the indication being vaginal hemorrhage. The placenta was found attached to the lower uterine segment anteriorly, with a portion of it growing into the posterior wall of the bladder through the rent in the uterus. The patient died on the table of hemorrhage. Microscopic study of sections from the bladder wall confirmed the gross findings. A fourth case has recently been observed by E. G. Waters.

CASE REPORT

Mrs. E. P., 20 years of age, white, para i, gravida ii, was admitted to Bellevue Hospital with a history of having undergone a low flap cesarean section on the same service one year previously, the indication being a generally contracted pelvis. The operation was done by Hervey C. Williamson under local anesthesia and no difficulty was encountered. The uterus was incised vertically, and the incision limited to the lower uterine segment. Following the delivery of a normal baby, the uterine incision

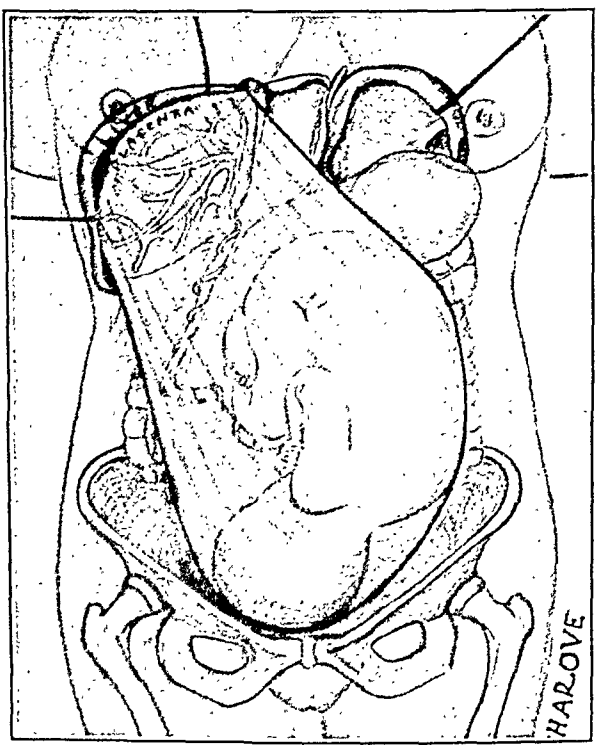


Fig. 1.—The placenta is attached to the right lobe of the liver, and to the gall bladder. The fetus is lying in intact membranes.

was closed in two layers with catgut. The patient had a morbid postoperative course, with foul lochia and some superficial infection of the abdominal wall. This condition cleared up and the patient was discharged as cured on the sixteenth day after operation. Pelvic examination at this time and several weeks later revealed no abnormal findings. Such was the course of her first confinement.

The present, or second pregnancy, began less than a year later, and the patient applied to the clinic, where she was found to have a second normal intrauterine gestation. The pelvis was otherwise negative. Subsequent visits were few and irregularly spaced, due to lack of cooperation from the patient. No complaints were recorded at any of these visits.

The patient's second admission to Bellevue Hospital was four weeks after the expected date of her second confinement. She was admitted complaining of a few mild, cramplike pains in the lower abdomen. No vaginal discharge was present. The fetal heart sounds were heard by the interne, resident, and attending obstetricians. Abdominal examination revealed a large fetus lying in a normal position with the

head floating. All the signs and symptoms of a mild pre-eclamptic toxemia were present. In view of this and the previous cesarean section for pelvic disproportion, no vaginal examination was done. The patient was prepared and sent to the operating room, at which time the fetal heart sounds were again found to be normal. Unfortunately, an emergency call from the ward necessitated delaying the operation for about one and one-half hours. When this emergency had been taken care of, the patient was routinely examined again, but no fetal heart sounds could be heard. It was decided to carry out the operation as planned.

When the abdomen was opened a large fetus was found lying in intact membranes directly within the parietal peritoneum. The membranes were ruptured artificially and the fetus delivered. No heart sounds were present. The fetus was perfectly normal in appearance, no evidence of maceration being observed. It was apparent that death had taken place only a short time before. A placenta of normal size was found intimately adherent to the liver and gall bladder. Removal not being feasible, the placenta was not disturbed except to prove definitely that it was firmly attached. There was no blood in the abdominal cavity. The uterus was found to be

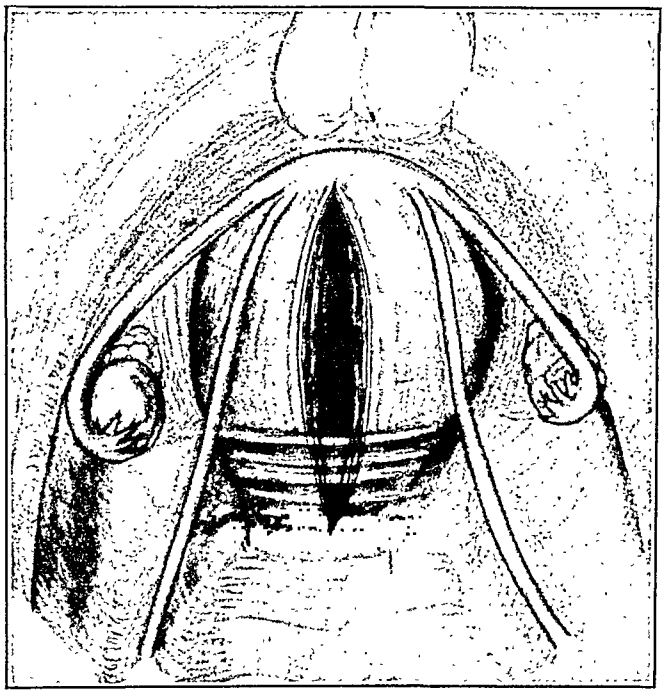


Fig. 2.—Illustrating the extent and location of the rupture of the anterior wall of the uterus.

enlarged to the size of a three months' gestation, with the anterior uterine wall split completely open from the lower angle of the previous low flap cesarean scar to the upper third of the fundus. The edges were everted and dry, so that the rupture was obviously an old one. The operator's fingers were introduced through the rupture into the cavity of the uterus, which was empty. The edges of the ruptured area were freshened with a scalpel and then sutured together with three layers of chromic catgut. The abdomen was closed in layers.

The patient's postoperative course was normal except for profuse drainage from the upper angle of the wound where the umbilical cord had been brought out of the abdominal cavity. This drainage, which resembled degenerated placental tissue, continued for about five weeks, after which the small opening healed spontaneously. Several subsequent examinations, both pelvic and abdominal, failed to reveal any masses.

In questioning the patient again after this second operation, the following history was elicited. The patient had a normal pregnancy until she accidentally fell from a stepladder a distance of some six feet. She struck the floor in a sitting position, arose, and a few minutes later experienced a sharp pain in the lower abdomen. This

was sufficiently severe to force her to go to bed and remain there for four to five days, but not marked enough to cause her to seek medical aid. This, she thought, occurred at the fourth month, but the date could not be definitely ascertained either from the patient or the ante-partum clinical records. Following this she experienced some indefinite abdominal discomfort for several weeks, none of which was referred to the upper abdomen. About six weeks following this accident she returned to the clinic and was examined, but nothing unusual was discovered. Her pregnancy continued in an apparently normal manner, until, as stated before, she voluntarily entered the hospital because of some lower abdominal cramps, and the rupture was discovered at operation.

It is interesting to note that this patient again became pregnant and was delivered by a low flap cesarean section about one year after her discharge from the hospital following the above described rupture. At the time of this third and final cesarean section the abdomen was found to be clean, free of adhesions, the uterus well healed, with no evidence of any thinning or weakening along the line of the previously ruptured cesarean scar. A normal baby was delivered at this time, the operation being done before the onset of labor. No part of the placenta from the previous pregnancy was found. The patient was sterilized by the Pomeroy technique.

SUMMARY

Low flap cesarean section does not prevent rupture of the uterine scar in a subsequent pregnancy, but does decrease greatly the probability of that accident occurring. Available statistics indicate that it occurs only 1/16 as frequently as in patients having the classical type of operation. The predisposing causes seem to be, (1) infection following the previous operation, (2) improper suturing of the wound, and (3) insertion of the placenta at the site of the previous low flap cesarean section scar.

A case is reported in which the uterine scar of a previous low flap cesarean section presumably ruptured early in pregnancy as the result of trauma, the product of conception being completely expelled into the abdominal cavity, where it developed four weeks past term as a secondary abdominal pregnancy. Suture of the ruptured uterus at this time resulted in good union, so that a subsequent pregnancy was carried to term. Extensive and careful search of the literature has revealed no similar case.

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DISCUSSION

DR. ALFRED C. BECK.—I have yet to see a rupture of the scar following a low cesarean section in labor, much less in pregnancy. That is a rather remarkable fact when one considers that the low section was originally restricted to those cases in which labor had been rather prolonged, in which many vaginal examinations had been done or in which the membranes had been ruptured for a long time.

When infection was present, no doubt the uterine wound broke down in places and a sinus was formed which drained through the lower angle of the abdominal incision or back through the lower segment and cervix into the vagina. That such a sinus has developed was demonstrated in several cases that I have cared for. In these when the bladder was peeled off at a subsequent section, a small opening was

revealed. In spite of the fact that these openings when present constituted a defect in the lower uterine segment, rupture did not take place in the subsequent pregnancy.

DR. HAROLD C. INGRAHAM.—I would like to ask the doctor what incision was made in these cases, whether transverse or linear.

DR. ELIOT BISHOP.—The only instance I can recall where a presumable rupture of a low flap cesarean scar occurred was one from Dr. Beck's clinic. This patient, in her first labor, had a 9-pound baby which was subjected to craniotomy, and in her second labor she had a 5-pound baby which was delivered by cesarean section, which according to the records reported to us had been of the low flap type.

The patient to whom I have referred was hospitalized only a few days before term. The operation was planned for 8:00 A.M. At about 3:00 A.M. one or two pains occurred and then the patient went into shock. She was sectioned, transfused, and recovered. The baby had been extruded into the abdominal cavity and was dead.

I was very much interested last June while in London, to note how commonly most of the men there used buried silk or linen sutures in their gynecologic cases and apparently in most of the cesarean sections also. Mr. Eardley Holland's well-known investigation of hundreds of ruptures of the scar following cesarean section stimulated Mr. Leslie Williams to search the literature but he found *no* case of rupture of the scar where the uterus had been repaired with nonabsorbable sutures.

DR. E. EVERETT BUNZEL.—We have had in the last year and a half three cases of rupture following the low flap section, at Sloane Hospital. One of these cases was previously done at Sloane, one at Bellevue Hospital, and one in an institution whose name I have forgotten.

Dr. Gepfert said that his case was one of ante-partum rupture, and yet he stated that this patient was uncomfortable for several hours prior to the time that the rupture occurred. Possibly those uncomfortable hours were beginning pains of labor. In other words, it may have been not an ante-partum but an intrapartum rupture.

DR. WILLIAM E. STUDDIFORD.—The extension of the rupture into the upper uterus, noted by Dr. Gepfert would suggest that at the time of the first cesarean section the incision had not been completely confined to the lower uterine segment. I am certain also that in a case quoted by Dr. Bunzel, the incision partly involved the upper uterine segment. When she was admitted to Bellevue Hospital, she was in the eighth month of pregnancy, and was not in labor. She had a complete separation of the placenta following an automobile accident, and it would have been very unusual for her to have a lower uterine segment sufficiently developed at this time to permit delivery.

About two years ago we had a most illuminating case at Bellevue Hospital which illustrated very well the relative healing qualities of an incision in the upper segment of the uterus and in the lower uterine segment. This patient had been in labor for about ten hours with ruptured membranes, and because labor had come to a standstill it was decided to do a low flap section on her. At the time of operation an incision was made in the lower segment of the uterus, when the patient began to show evidence of shock, and because the operator was hurried, the fetus was delivered as a breech. In doing this he extended the incision up to the top of the fundus of the uterus, so that, in effect, he had two incisions in the same uterus, a low flap incision which he made with a knife, and a classical incision which was caused by extension. The patient ran a febrile course for two or three days, but did not seem to be in particularly bad condition. On the fourth day, however, she suddenly presented all the signs and symptoms of general peritonitis and died about the tenth day after operation. At autopsy it was found that the low flap incision had healed by primary union. The tear which had passed through the contractile part of the uterus was wide open so that there was a large fistula from the uterus into the peritoneal cavity.

It seems fairly easy to explain this. An incision which is made in the lower uterine segment passes through tissue which is relatively quiescent, noncontractile, and even if catgut is weakened by a low-grade infection, it has a very marked

tendency to heal. When we have an incision through the contractile part of the uterus, however, the very contractions, in the face of weakened catgut and of infection tend to break this part of the uterus open.

DR. VINCENT P. MAZZOLA.—About twelve years ago I performed a low double flap cesarean section on a patient with contracted pelvis and membranes ruptured for many hours. On the tenth day postoperative, the patient passed the entire line of sutures per vaginam. Two years later she became pregnant again. An elective low double flap cesarean section was done after a short period of labor. After peeling off the lower flap, examination of the old scar revealed perfect union. This single experience impressed me with the fact that although the entire row of sutures had previously been passed ten days postoperative, the low section scar healed with primary union and hence was less liable to rupture.

DR. WILLIAM H. CARY.—I would like to ask the doctor if he will elucidate what happened to the placenta in this case. I understand it was left attached to the gall bladder and the liver.

DR. GEPFERT (closing).—We made a point of looking up the relative figures on transverse and vertical incisions. The only two things that stand out are that in using the vertical incision there is a little tendency to tear into the muscular part of the uterus during the delivery of the head and shoulders. In doing the transverse incision there is a tendency to profuse bleeding in the lateral extensions. As far as the relative occurrence of rupture goes, there seems to be no difference between the two modifications of the technic.

In answer to Dr. Bunzel, I would say that we have no definite way of knowing just when this woman ruptured her uterus. We believe she ruptured it sometime during the third month, otherwise we would not expect to get a complete transference of the placenta. The placenta was definitely attached to the liver and to the gall bladder and was not free in the abdominal cavity. The edges of the uterine rupture were dry and everted. There was no free blood and very little fluid in the abdominal cavity. On that basis, we presumed that the rupture was a very old one and that the woman had a true secondary transplantation, and abdominal pregnancy. In this case the umbilical cord was brought out through the upper angle of the incision. Drainage persisted for about five weeks.

PUERPERAL STERILIZATION

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DURING the last fifteen months at the Chicago Lying-in Hospital, 50 women have been sterilized by tying off the Fallopian tubes within the first twenty-four hours after delivery. The average number of hours elapsing between the delivery and the operation was 11.5; the shortest time was 1.5 and the longest 23.5 hours.

Skajaa[1] has reported 126 puerperal sterilizations done between the second and twenty-ninth post-partum days. His report covers a five-year period. There is a series of 46 patients who were operated upon between the fifth and twenty-ninth post-partum days. In this group, there were 7 cases of thrombosis and one of embolism, an incidence of over 17 per cent. Thrombosis was especially frequent where the operation was performed five or six days post partum. In a group of 12 cases done on the fifth and sixth post-partum days, there were 4 cases of thrombosis

and 1 of embolism, an incidence of over 41 per cent. He included in his report a series of 80 patients operated upon between the second and fourth days post partum. In this group, there was only one case of thrombosis, an incidence of 1.25 per cent. He enumerates the following probable etiologic factors for thrombosis: (1) less satisfactory general condition of the patient, (2) the use of ether instead of local anesthesia, (3) complicated labor with artificial delivery, (4) post-partum hemorrhage with insertion of hand in the uterus, and (5) demonstrable infection previous to operation.

The morbidity and mortality of our 50 cases of puerperal sterilization are compared with those of a series of 465 cesarean sections and sterilizations. There were 399 lower segment, 7 classical cesarean sections with sterilization, and 59 Porro cesarean sections. The standard of febrile morbidity advocated and approved by the American Committee on Maternal Welfare was used in calculating the morbidity. This standard is as follows: any patient with a temperature of 38° C. (100.4° F.) or over, recorded on any two days after the first twenty-four hours post partum, oral temperature readings being made at least 4 times daily, is regarded as febrile. The incidence of febrile morbidity in the 50 cases of puerperal sterilization was 6 (12 per cent). The maximum temperature was 101.5° F. and not one of the febrile cases had a fever which lasted more than two days. The febrile morbidity in the 7 classical cesarean sections was 85.7 per cent; 59.5 per cent of the Porro cesarean sections were febrile, and 40 per cent of those having a lower segment cesarean section had a febrile reaction. The average morbidity for all types of sterilization combined with cesarean section was 43 per cent, in comparison with 12 per cent morbidity in the present series.

The average period of postoperative hospitalization was 11.3 days. The febrile cases were discharged between the ninth and fourteenth postoperative days. In the whole series there were two minor wound infections which healed rapidly. Both of these patients were afebrile. They were discharged on the thirteenth and fourteenth postoperative days, respectively. There were no deaths in the cases of puerperal sterilization, whereas in the cesarean section and sterilization group, there were 4 deaths, an incidence of approximately 1 per cent.

Labor was induced medically in 10 per cent of these patients at or near term. This was done because of some maternal complications which rendered the continuation of the pregnancy undesirable. One of these patients had a febrile morbidity.

The average parity of the patients was 4.6. The average age of these women was 29.5 years; the youngest was 20 years old, the oldest 42. The former patient was a cardiac with mitral insufficiency, and she had three other living children. A local anesthesia was used exclusively in these 50 cases. The usual preoperative medication consisted of ¼ gr. of morphine and $\frac{1}{150}$ gr. of scopolamine given 1¼ hours preoperatively and ⅙ gr. of morphine and $\frac{1}{200}$ gr. of scopolamine given one-half hour preoperatively. The dosage was varied somewhat depending on the size of the patient, those of lighter weight being given a smaller dose than those of heavier weight.

However, in cases of cesarean section with sterilization, preoperative medication with barbiturates and morphine is not used frequently in conjunction with local anesthesia because of the excitation of the patient and the possible effects of these drugs upon the fetus.

The technique of the operation is relatively simple: local infiltration anesthesia with 0.5 per cent novocaine solution is used in the abdominal wall and within the peritoneal cavity. A small median incision is made immediately below the umbilicus. The round ligament is grasped with the fingers, exposing the uterine horn together with the tube. The Fallopian tube is gently grasped with Allis forceps and 1 to 2 c.c. of a 0.5 per cent novocaine solution is injected between the leaves of the mesosalpinx. The tube is kinked by pulling it forward with the Allis clamp. The tube is then clamped on both sides of the Allis forceps and then crushed about 1 cm. on either side of the forceps with a hemorrhoidectomy clamp. Black silk and catgut have both been used by passing the suture through the mesosalpinx, and then tying it tightly over the crushed areas of the tube. The opposite horn of the uterus is exposed and the tube is treated in the same manner.

Puerperal sterilization has many advantages. We have tried this procedure to determine its efficacy and safety as compared with other means of sterilization. The carrying out of this procedure within twenty-four hours after delivery avoids the questionable procedure of cesarean section for sterilization and the necessity of subsequent hospitalization and operation for sterilization. It also avoids the loss of time and the expense of the subsequent hospitalization period. The period of hospitalization subsequent to delivery is not prolonged more than one or two days. In analyzing our cesarean sections, it was found that many of them were done where sterilization was an important consideration and was used as an indication for the procedure. Doubtless, similar conditions exist in other clinics and institutions. Obviously, our series is not large enough to draw any final conclusions relative to the desirability and safety of this operation as compared with other procedures for sterilization. In this group of cases there was no indication for cesarean section other than sterilization.

Most of the women were multiparas and the average duration of the labor was approximately seven and one-half hours. There were only 6 cases where labor was more than ten hours and in 1 the labor was less than one-half hour. These cases were selected with very great care and every effort was made to eliminate those who had a potential genital infection. There were no cases of mechanical induction of labor. All genital manipulations prior to or during labor were considered as hazards and such cases were automatically excluded. Where there was danger of the introduction of infection, either ante partum, intra partum, or post partum, from procedures, such as difficult operative deliveries, manual removal of the placenta, post-partum hemorrhage, etc., puerperal sterilization was not done.

In the whole series of cases the average length of time which elapsed between the rupture of the membranes and the delivery was 5.1 hours, though 3 patients with membranes ruptured for more than forty hours

showed no morbidity. There were 6 deliveries with low forceps, 1 of which was febrile. The other patients delivered naturally.

There is practically nothing in the literature relative to the puerperal sterilization. F. E. Whitacre, formerly of our staff, suggested the procedure of sterilization immediately following delivery. Not being in favor of subjecting recently delivered women to such an operation immediately after the termination of labor, the above procedure was adopted.

The following outline gives the indications for which puerperal sterilizations were done:

	CASES
Cardiac (27)	
Rheumatic heart disease with insufficiency	26
Congenital heart disease	1
Cardiovascular (4)	
Hypertensive heart disease	1
Rheumatic heart disease with pre-eclampsia	1
Chronic glomerulonephritis with cardiac disease	1
Essential hypertension	1
Chronic infectious diseases (6)	
Pulmonary tuberculosis	5
Chronic bronchitis with marked arthritis	1
Constitutional diseases (3)	
Diabetes	1
Thyrotoxicosis	1
Anemia of pregnancy (with previous post-partum hemorrhage)	1
Neurologic diseases (7)	
Spastic paraplegia with rheumatic heart disease	1
Epilepsy	4
Mixed psychoneurosis	1
Paralysis of lower extremities	1
Vascular diseases (1)	
Marked vulvar varicosities	1
Cardiovascular renal disease (2)	
Chronic nephritis	2
Total	50

It is to be emphasized that in our series of cases there has been neither thrombosis nor embolism.

Recently, E. F. Daily analyzed 1,000 cesarean sections of all types in the Department of Obstetrics and Gynecology at the Chicago Lying-in Hospital. This series was divided chronologically into two groups of 500 each. There were 182 cesarean sections and sterilizations in the first 500 cases as compared with 217 in the second 500 cases. The number and percentage of the cases in which the indication for sterilization was a decisive factor showed an increase of 15 per cent. The major indications of this group were chronic cardiac and other organic diseases. If one considers cardiac disease alone, there was an increase of 97 per cent in the second series of cases over the first series, in which the operation was done largely because of the indications for sterilization. In the chronic nephritic group there was an increase of 143 per cent in the second series as compared with the first. There was an increase of 2.7 per cent of

febrile morbidity in the second series of cesarean sections with sterilizations over the analogous cases in the first group.

Of the 406 cesarean sections and sterilizations, 287 were done by the Madlener technique and 119 by resection of the tubes. In comparing the first 500 with the second 500 cesarean sections, there was a decrease of tubal resection from 74 to 45 cases, a drop of 40 per cent. The use of the Madlener technique increased 56 per cent. In our series only one case was done by means of tubal resection. The others were done by the Madlener technique.

We are inclined to believe that this is both a desirable and safe procedure in women who are neither actually nor potentially infected by genital manipulations prior to or during labor. Unless other indications actually exist for performing cesarean sections, we are of the opinion that it is better to follow natural delivery with this method of puerperal sterilization than to resort to cesarean section.

It is in patients who have a natural delivery, particularly in multiparas with rather short labors, that puerperal sterilization within twenty-four hours is indicated.

CONCLUSIONS

We have made a preliminary report of 50 cases of puerperal sterilizations performed within twenty-four hours after delivery. The morbidity and mortality of these patients are compared with those of patients who were subjected to cesarean section with sterilization. Preoperative basal anesthesia with local infiltration anesthesia was used exclusively in carrying out the technique of this operation. We are eliminating cesarean sections for sterilization. The cases were carefully selected and potential infection was regarded as a contraindication to the performance of puerperal sterilization. This operation may be considered as a desirable substitute for late sterilization. In case no contraindications exist, it is performed within twenty-four hours subsequent to delivery. At the present time we are of the opinion that puerperal sterilization, subsequent to the first twenty-four hours after delivery, is not a desirable procedure and that the necessity of sterilization should not lead us to perform a cesarean section in the absence of other indications.

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Krusen, Randall, and Stuhler: Fever Therapy Plus Additional Local Heating in the Treatment of Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. 22: 185, 1938.

The authors found that in women in whom a pelvic inflammatory disease proved refractory to fever therapy alone, the addition of local pelvic heating in conjunction with fever therapy produced most encouraging results.

With proper preparation and follow-up treatment, single ten-hour sessions of fever therapy at 41.5° C. (106.7° F.) will produce negative cultures in a high percentage of cases of gonorrhea.

C. O. MALAND

GRANULOMA VENEREUM OF CERVIX UTERI

A Statistical Study

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THE cervix uteri is now recognized as a site for the lesion of granuloma venereum (inguinale), either with or without ulcerations elsewhere.[1] This exuberant granulomatous ulceration of the cervix simulates carcinoma so closely that the diagnosis is usually made only after histologic study of a biopsy. The frequency of this specific condition has never been determined, yet granulomas of the cervix have been described since 1928. Gardner[2] suggested that such granulomas may possibly be related to granuloma inguinale (venereum). In 1934 McGee[3] reported eight cases of cervical granuloma, in none of which was he able to demonstrate Donovan bodies. He classified these lesions as a nonspecific granuloma but observed that five of his patients responded favorably to treatment with tartar emetic. It is interesting to note that his patients were negroes, from 19 to 60 years of age, and in each a tentative clinical diagnosis of carcinoma was made.

Granuloma venereum (inguinale) of the cervix was not established as a definite entity until 1937[1] and it was then observed that the Donovan bodies had an affinity for silver. This observation followed a previous description[4] of a specific histology for granuloma venereum and a pathognomonic cell was discerned. In regard to granuloma venereum of the cervix, questions now arise as to its numerical, racial and age incidence; symptomatology; its association with ulcerations elsewhere. We have reviewed all sections of cervices which have been examined in our laboratory for the past ten years. The criteria for the diagnosis were based upon the observations made in a former article.[4] In all cases that were accepted as positive, the pathognomonic cell was observed. This is a large cell which contains intracytoplasmic cysts; and the round or rodlike Donovan bodies are grouped peripherally within the cysts.

From our previous studies on venereal diseases we have recognized histologic characteristics which frequently enable us to diagnose, in addition to granuloma venereum, lymphogranuloma venereum and chancroid.[5] In lymphogranuloma venereum there is pronounced peritubular infiltration with plasma cells and lymphocytes, accompanied by fibroblastic activity, dilated lymphatics, and in some cases with giant cells of the foreign body type. Occasionally foci of suppuration are noted, similar to that type of reaction seen in buboes, necrotic centers surrounded by macrophages. The chancroid is characterized by superficial necrosis infiltrated with polymorphonuclear leucocytes. In the surrounding area plasma cells, lymphocytes, and endothelial leucocytes are also present. There is an acute peri- and endovasculitis with pronounced swelling of the endothelium, frequently blocking the lumen of the capil-

laries and leading to necrosis. The vascular changes are characteristic and responsible for the superficial necrosis and unhealthy granulation.

We were unable to find a single case of granuloma venereum of the cervix in the files prior to 1934. However, since 1934 nine cases were observed. This confirms the impression shared by our colleagues that venereal granuloma is on the increase. The 9 cases were found in the 830 biopsies of the cervix which were performed between Jan. 1, 1934, and March 31, 1938. This is 1.1 per cent of all cervices that were biopsied. Of these 830 patients, 694 were white and in none was the diagnosis of granuloma venereum made. Of the biopsies from the 136 negro patients, 9 were positive for granuloma venereum, an incidence of 6.6 per cent. If the 69 carcinomas are eliminated from this group, we find that 13.4 per cent of the remaining 67 negro patients who complained of cervical lesions, suffered from granuloma venereum.

No especial age incidence could be established from this small group. Like McGee's patients with nonspecific granuloma, ours varied in age from 18 to 62 years. It does occur (Table I) most commonly in the periods of sexual activity, thus lending support to the assumption that this is a venereal disease.

TABLE I. SYMPTOMATOLOGY

AGE	ULCERATION	TESTS	PREGNANCIES	DISCHARGE	BLEEDING	ABD. PAIN	LOSS OF WEIGHT	BACKACHE	DURATION	RED CELLS IN MILLIONS	HG
18*	Vulval	Chanc. + Frei −	Now pregnant							2.9	56%
20	Vulval	None	0	+		+		+	1½ yr.		50%
22	Vulval	Wass. − Chanc. + Frei +	?	+					1 yr.		
27	None	Wass. − Kahn −	2	+		+			9 mo.	2.5	70%
33*	None	Wass. + Chanc. + Frei +	3	+	+				4 wk.	3.9	70%
39	None	Chanc. + Frei −	9	+		+			2 mo.		
47	None	None	0	+	+				3 mo.		
56	None	Wass. −	3	+	+		+		3 mo.	4.1	74%
62†	Inguinal and vulval	Wass. − Frei − Diabetic	3	+					2 yr.	3.9	70%

*Reported previously by Pund and Greenblatt.
†Reported previously by Dr. M. E. Ross.

SYMPTOMATOLOGY

The duration of complaints, from which the patients sought relief, varied from two months to two years, with an average of eight months. Eight patients complained of vaginal discharge and in 3 of these the discharge was blood stained.

Three suffered some pain in the lower abdomen, 1 complained of backache, and 1 had lost weight. The 6 hospitalized patients exhibited a varying degree of anemia. It is interesting to note that these symptoms suggest carcinoma, and in 5 this was the presumptive clinical diagnosis. A presumptive diagnosis of granuloma venereum was made in four instances. These 4 patients were seen in the past two years while a group study of the venereal diseases was being conducted at the University of Georgia School of Medicine.

Five of the patients had borne children, and 1 of the remaining 4 was pregnant. Four patients were tested with Frei and chancroid bacillary antigens. Two of these had positive chancroid tests and in one of these the histologic lesion suggested chancroid as well as venereal granuloma. The other 2 patients reacted positively both to the chancroid and Frei antigens, and in both of these the histology suggested chancroid. One patient, a diabetic, was tested with Frei antigen and did not react. She, however, had a history of a previous bubo. Four patients were not tested for venereal lymphogranuloma or chancroid. The histologic lesion of one suggested lymphogranuloma venereum and the ulcerations were accompanied by elephantiasis of vulva. One had a history of gonorrheal infection; one had previously been operated upon for pelvic inflammatory disease; and in the section from the fourth patient, the histology suggested granuloma venereum complicated with chancroid.

In our experience, multiple infections[5] are so common that we believe that granuloma venereum usually occurs superimposed upon other conditions. The histories, physical findings, and histology suggest that this disease in most of these patients was superimposed upon gonorrheal cervicitis, chancroidal infection or lesions of lymphogranuloma. The lesion was limited to the cervix or cervix and vagina in 5 cases, and in 3 to the cervix alone. In the other 4 cases, ulcerations were also present on the vulva, and in only 1 was an inguinal ulceration present.

SUMMARY

From a study of 830 biopsies of diseased cervices of the uterus, the lesion was due to granuloma venereum in 9 cases, an incidence of 1.1 per cent.

In biopsies from negro patients the incidence was 6.6 per cent.

In biopsies from negro patients without carcinoma of the cervix, the incidence was 13.4 per cent.

We have never observed granuloma venereum of the cervix in a biopsy from a white patient.

Nine cases of granuloma venereum of the cervix have been found since 1934. No cases were observed six years prior to 1934.

The cervix uteri may be the primary site of granuloma venereum, and is often a complication of other venereal diseases.

The symptoms suggest carcinoma.

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THE BLOOD CHEMISTRY IN ERYTHROBLASTOSIS FETALIS

Report of Three Cases With Abnormal Findings

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ERYTHROBLASTOSIS fetalis is still an obscure enough disease to merit reporting any new findings which might throw light on its pathogenesis, symptomatology, or treatment. With this in mind I wish to report three proved cases with distinctly unusual blood chemistry findings.

In a brief review of the literature including the classical reports of the disease,[1-3] I found no reference to unusual findings in the blood urea, blood uric acid, and blood chloride values. Moreover, the conclusions as to the serum protein values are not in agreement. The clinical, hematologic, and pathologic pictures are fairly uniform in all cases, but except for the bilirubin determinations the other chemical determinations seem to have been overlooked. The reason for this is probably the technical difficulty in obtaining sufficient blood from newborns for complete analysis. In addition possibly usual changes were not suspected or present.

REPORT OF CASES

The following three cases were all seen at the Sinai Hospital, Baltimore, Maryland:

Case 1.—Baby E. The sixth gestational product of Mrs. E., aged 31, whose previous pregnancies terminated as follows: (1) Normal full-term parturition at Sinai Hospital. Child alive and well aged 11 years. (2) Full-term parturition, child developed jaundice and died at Johns Hopkins Hospital at the age of one month. No autopsy record was obtained; the diagnosis was icterus gravis. This was in 1926 before erythroblastosis was recognized as a clinical entity. (3) Full-term stillborn at Sinai Hospital; cause of death not determined. (4) Premature infant that lived three days. (5) Full-term stillborn, intranatal death. This labor was induced by 25 gr. of quinine. This was thought to be a possible cause for intrauterine death.

During the pregnancy now under consideration a thorough study for the cause of the fetal deaths was made. Diabetes mellitus was excluded by a normal blood sugar and a normal glucose tolerance test as well as by the absence of glycosuria. Syphilis was eliminated by a negative Wassermann and Kahn reaction. However, on the advice of the syphilologist one course of the antisyphilitic therapy was given in the early part of pregnancy. The patient exhibited no evidence of either early or late toxemia. In view of the patient's story that towards the end of each preceding pregnancy, she had noticed that in the last month the fetal movements became less pronounced and finally ceased, it was decided to admit her for induction of labor, without quinine, three weeks before term. Labor was induced and the delivery was normal.

At birth the child cried immediately and respiration was established spontaneously. The vernix was scant and white and the placenta was normal in size and consistency. The characteristic thick yellow vernix caseosa was not present. The delivery was at night and in the artificial light no jaundice was noted. Eight hours after delivery the child developed jaundice. Hematologic study revealed an erythroblastic anemia with characteristic findings. The hemoglobin was 90 per cent, red blood count

3,350,000 per c.mm., with a color index of 1.3. The acetic acid residue showed 80,000 nucleated cells of which 45,600 were nucleated red cells and 34,000 were leucocytes. The Schilling differential showed 15 per cent early white cells, mostly myelocytes and mestamyelocytes, 45 per cent polymorphonuclear neutrophiles, 30 per cent lymphocytes, 8 per cent monocytes, 2 per cent basophiles. The nucleated red cells were macronormoblasts and normoblasts. The red cells in the smear showed

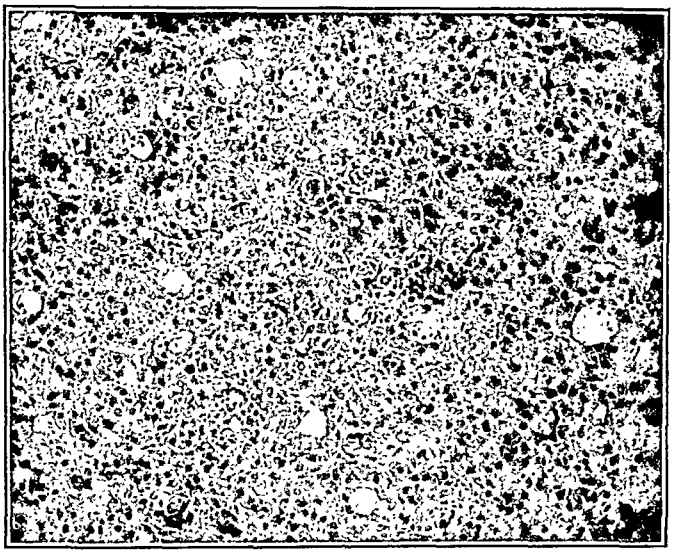


Fig. 1.—Baby E. Erythroblastosis with icterus gravis. Section of the liver showing foci of erythroleucoblastic activity. Deposits of hemosiderin were numerous.



Fig. 2.—Erythroblastosis with icterus gravis. Section of thymus showing typical macronormoblasts growing in an extramedullary focus of blood production.

anisocytosis with predominance of macrocytes. The clotting and the bleeding time were within normal limits. The platelets were moderately reduced. The fragility test was normal. The Wassermann test was negative and the roentgenologic examination of the long bones failed to show syphilis. The icterus index was 100, and the van den Bergh bi-phasic. The gastric contents (vomitus) revealed bilirubin, ruling out biliary obstruction. The urine had a trace of bilirubin and urobilin. The stools were positive for bilirubin and urobilin.

The child had an enlarged spleen and liver and, in a few days, developed rigidity of neck and limbs. During the following eight days the jaundice became more intense, pallor appeared, and the anemia became progressively worse. However, the nucleated red cells gradually became less numerous and by the tenth day were entirely absent. At this time the icterus index was 150 and the urea was 200 mg. per cent.

The child was treated with a concentrated formula, daily clyses of 5 per cent glucose, and repeated blood transfusions, but on the eleventh day developed a temperature of 103° F., with physical signs of pneumonia, and died. A complete autopsy grossly revealed bile stained viscera, a liver of 200 gm. and a spleen of 50 gm. The lungs presented evidence of pneumonia complicated by hemothorax. Microscopic examination of the viscera demonstrated extramedullary foci of active hematopoiesis in the liver, spleen, kidney, pancreas, adrenals, thymus, pituitary, and lymph nodes. These foci on examination presented areas of erythroleucoblastic activity. Hemosiderin deposits were found in the liver and spleen.

This case is noteworthy for the definite familial history and the blood urea of 200 mg. per cent.

CASE 2.—Baby B. First pregnancy. At thirty-six weeks the mother developed hydramnios, edema, and dyspnea. This was so marked that we considered the possibility of interruption. The urine showed a one-plus albumin. The phenolsulphone-

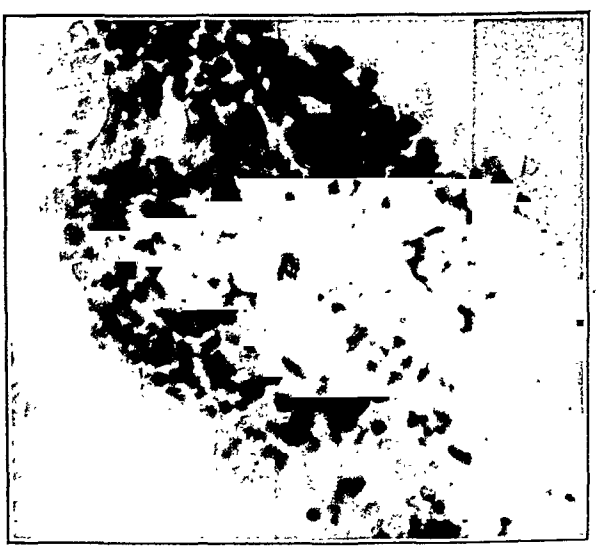


Fig. 3.—Section of the bone marrow showing abnormal number of erythroblasts.

phthalein test showed 65 per cent recovery in two hours. The blood chemistry was essentially normal: Urea 24 mg. per cent, chloride 371 mg. per cent, and total serum protein 7.8 mg. per cent, with an albumin globulin ratio of 2. The uric acid was elevated to 5.3 mg. per cent. The maternal Wassermann reaction was negative. The hydramnios and edema failed to respond to conservative treatment and the pregnancy was interrupted at thirty-six weeks by medical induction followed by artificial puncture of the membranes. Labor was uncomplicated and the second stage was terminated by an episiotomy and low forceps delivery of a live female child which weighed 6 pounds 12 ounces. The general condition of the child was poor. The temperature was 96° F., the heart action slow and irregular, cry weak, and respirations slow and shallow. It was quite difficult to resuscitate and intratracheal aspiration, water baths and artificial respiration, followed by intratracheal insufflation with a resuscitator were necessary before the infant was breathing regularly. The infant kept expectorating frothy sputum.

Physically the infant presented generalized anasarca involving especially the face, hands, feet, and chest. The skin was pale and cyanotic. The heart was not enlarged and there were no murmurs. The chest presented diffuse moist râles. The abdomen presented physical signs of ascites. The liver, spleen, and kidneys were not palpable.

There was marked vulval edema and the extremities had pitting edema. The placenta was large and friable but the vernix was normal in color and consistency. A hematologic study revealed a macrocytic anemia. The hemoglobin was 75 per cent. The red blood count 2,960,000. The color index was therefore 1.25. The total acetic acid resistant count was 7,600 with 34 per cent of them nucleated red cells. The Schilling differential count showed 47 per cent polymorphonuclears, 44 per cent lymphocytes, 1 per cent monocytes, 6 per cent myelocytes, and 2 per cent juveniles. The urine was scant, with one-plus albumin and 5-6-plus cells per high power field. The blood chemistry was again abnormal. The urea was 40 mg. per cent and the uric acid 8.5 mg. per cent. The chlorides were 144 mg. per cent. The serum protein was 7.4 per cent with an A/G ratio of 4.3. The blood Wassermann reaction was negative as were the x-rays of the long bones.

The infant was placed in a heated crib with continuous pure oxygen supply interrupted by frequent carbon dioxide inhalations. Whole blood was given intramuscularly but the infant became gradually worse and died within twelve hours. A few hours before death, 0.5 c.c. of mercupurin was given intramuscularly but failed to exert any manifest action before death. The autopsy grossly revealed marked anasarca with particular edema of the face and the extremities, ascites, and hydrothorax. The viscera were pale and edematous but aside from that were grossly normal. The liver and spleen were small, weighing 120 and 5 gm., respectively. The kidneys were normal in size and shape. Microscopically, extramedullary blood production was evident in numerous organs. There were foci of active hematopoiesis of the erythroleucoblastic variety in the liver, spleen, thymus, pancreas, adrenals, lymph nodes, and bone marrow.

This case of hydrops is noteworthy chiefly because of the potential toxemic status of the mother combined with the unusual blood chemistry of the offspring.

CASE 3.—Baby F. First pregnancy. Delivered normally at term, weighed 7 pounds 6½ ounces, and was born jaundiced. The amniotic fluid was bile stained, and the vernix was thick and yellow but the placenta was normal. Physical examination revealed splenomegaly in addition to severe icterus. Within the twenty-four hours after birth the child developed dyspnea, cyanosis, and refused nourishment. A few hours later the child had marked hematemesis and moderate vaginal bleeding.

The blood count revealed a severe anemia with the color index slightly above one, the hemoglobin being 25 per cent and the red blood count 1,200,000 per c.mm. Smear and white count were not obtained. Blood urea was 60 mg. per cent. No other laboratory tests were done as the child died within twenty-eight hours after delivery. The only treatment given was whole blood intramuscularly and calcium lactate by mouth.

The post-mortem examination grossly showed a large spleen and hemorrhages into the kidney, uterus, serosa, and pericardium. Microscopically, the organs showed typical areas of extramedullary erythroleucoblastic activity.

This case is noteworthy only because of the typical clinical and pathologic findings, a very severe congenital anemia associated with icterus and the elevated blood urea.

COMMENT

In all three cases of erythroblastosis presented there were abnormal blood chemistry findings varying from slight nitrogen retention to uremia. The nonprotein nitrogen and blood urea were elevated in all three cases, and the blood uric acid was elevated in the first two. This is in favor of renal insufficiency as a significant factor in the fatal cases, at least, since all these three infants died. The six kidneys examined pathologically from these three cases failed to exhibit any organic changes of nephritis or nephrosis. It may be that in newborns, renal insufficiency may result from functional changes incident to a severe anemia, or secondary to an intercurrent infection or preceding death from erythroblastosis.

As regards the pathogenesis of erythroblastosis a suggestion as to the underlying difference in the clinical pictures of icterus gravis, hydrops fetalis, and congenital anemia is found in contrasting the clinical pathologic findings in these cases. In hydrops, although the nucleated blood cells in the peripheral blood were only moderately increased, the foci in the viscera were exceedingly plentiful, thus favoring the view that in hydrops fetalis the pathogenesis lies either in overgrowth of immature forms, or a failure of maturation of erythrocytes. However in icterus gravis in which the nucleated red cell count is higher, and the foci in the viscera less plentiful the etiology lies in the delivery of these immature forms to the circulation with resulting increase in destruction. Hellman and Hertig,[4] in a study of 13 autopsies on infants who died of hydrops fetalis and 6 on infants who died of icterus gravis, also found more extramedullary erythropoiesis in the former group.

The reason for the spasticity in nuclear icterus has never been fully explained even though pigmentation of the central nervous system has been observed. In Case 1, the infant developed spasticity and rigidity of the neck and limbs associated with azotemia. This uremia associated with acidosis may be responsible for the rigidity of the neck and limbs. This type of spasticity is very often seen in so-called nuclear icterus, the outstanding feature of which is the pigmentation of the cerebral nervous system, particularly the large ganglia. It is suggested that the azotemia associated with icterus gravis may be responsible for the central nervous system symptoms frequently found in nuclear icterus.

In explanation of the edema, in erythroblastosis with hydrops fetalis some authorities have stressed the albuminuria, decrease in total serum protein, and reversal of the A/G ratio as the cause. In Case 2 the albuminuria was slight, the serum protein normal, and the A/G ratio accentuated strongly suggesting another cause for the edema. The total urinary output was diminished and this oliguria combined with azotemia speaks for renal insufficiency as the cause of the edema. The low blood chloride is best explained by the loss of chloride with the edema, anasarca, and effusion fluids. The low chloride value is seen also in cases of nephritis with edema and in cases of nephrosis.

CONCLUSIONS

1. Azotemia is a frequent complication in severe cases of erythroblastosis of all types, and when present makes the prognosis much worse.
2. This azotemia may be the responsible factor in the central nervous system symptoms in nuclear icterus.
3. Renal insufficiency, per se, and not albuminuria and decrease in serum protein, is the more probable cause of universal edema of the newborn.
4. In the absence of signs of acute nephritis, mercurial diuretics along with blood transfusions and lyophile (concentrated human serum) seem to be indicated in treating the edema.

SUMMARY

Three fatal cases of erythroblastosis fetalis are presented, one with icterus gravis, one with hydrops fetalis, and one with congenital anemia,

all of which showed abnormal blood chemistry: azotemia, which is therefore regarded as an unfavorable prognostic sign.

The author wishes to thank Dr. Daniel Sondheimer, resident pathologist at Sinai Hospital, Baltimore, Md., for the pathologic examinations and for helpful suggestions in the preparation of this paper.

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PRECOCIOUS PUBERTY DUE TO AN OVARIAN CYST IN A FIVE-YEAR-OLD GIRL

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N. A., aged five years (Hospital Number E 6088), was first seen July 13, 1935, with the history of considerable breast development during the previous two months. On the day before consultation, the child while sitting on the toilet, announced, "Cherry juice is running down my legs." On inspection definite blood mixed with mucus apparently coming from the vagina, could be seen on the inner surface of each thigh. Subsequently a study of the visual fields and a roentgenogram of the sella turcica were done and revealed no abnormalities.

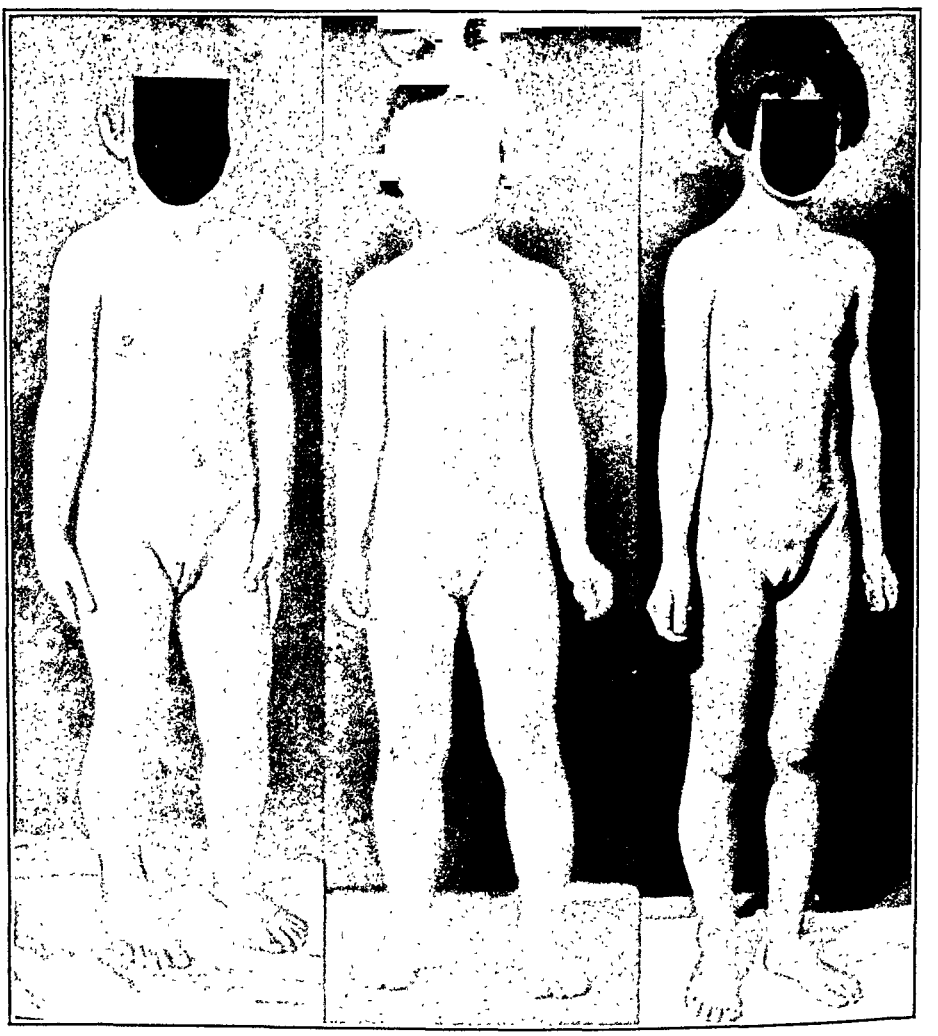
The breasts were definitely enlarged (Fig. 1, *A*) and the parenchyma was nodular and shotty. There was bloody mucus with a typical menstrual odor surrounding the vulva, and the external genitalia, although small and in proportion to the child's size, presented such adult characteristics as brownish pigmentation and well-developed and sharply-defined labia minora. In addition, the vaginal mucosa was not only unlike that of a prepuberal child but also was thrown into definite folds resembling rugae. There was no well-defined axillary or pubic hair although on close inspection a few scattered hairs could be seen on the mons veneris. Rectobimanual examination was done under anesthesia the following morning. The uterus was enlarged almost to the size of that of an adult virgin. There was a cystic, symmetric mass, the size of a golf ball, in the left adnexal region, but nothing was palpable on the right side. Biopsy of the vaginal epithelium taken at this time showed (Fig. 2) hyperplastic mucosa with a stratified, considerably thickened, squamous epithelium slightly cornified in some areas, and with a papillated basal layer.

Exploratory laporotomy was performed on July 16, 1935. The right ovary was small, the size of a navy bean, and its surface was smooth, presenting no follicles. It was the typical ovary of a child. The left ovary was replaced by a smooth, glistening cyst 4 to 5 cm. in diameter (Fig. 3). Both tubes were extremely long and tortuous and with the uterus were approximately of adult size. In fact, with the exception of the right ovary, all of the intra-abdominal genitalia presented adult characteristics. Careful palpation of each kidney and suprarenal area revealed nothing unusual. Left salpingo-oophorectomy with cornual excision and appendectomy were performed.

The report of Dr. H. P. Smith is as follows: "The left ovarian mass measures two and a half by four centimeters in diameter. The surface is smooth and beneath it can be seen several cysts three millimeters in diameter. On section several larger cysts are found. They are lined by a smooth yellow membrane. Microscopically the lining of the cysts is composed of polyhedral cells several cells in thickness. Some resemble granulosa cells; others have vacuolated cytoplasm, like that of lutein cells. The stroma between the cysts is of the normal mature type.

There is no evidence of malignancy. Ordinarily, cysts of this type are not regarded as being neoplastic. Disturbances in other glands of internal secretion, e.g., the hypophysis, might produce this effect. However, if this were true, it is difficult to understand why cysts did not form in the other ovary. Diagnosis: Granulosa cell cysts of left ovary.'' (Fig. 4.)

The convalescence was uneventful and to date (three years later) the child has been entirely well without recurrence and has been developing in an entirely normal fashion (Fig. 1, *B* and *C*). She has returned to the prepuberal condition of a normal female child with one exception; the breasts, although smaller, softer and less nodular, remain slightly larger than is to be expected of a girl eight years of age.



A. *B.* *C.*

Fig. 1.—*A*, Preoperative condition, aged 5 years; *B*, nine months postoperative; *C*, two and one-half years postoperative.

HORMONAL STUDIES*

The hormone content of the cystic fluid, of pre- and postoperative urine specimens, and of a urine specimen taken in January, 1938, was investigated. There were 1,000 rat units per liter of the estrogenic hormone in the preoperative urine specimen. Approximately 35 c.c. of fluid were aspirated from the extirpated cyst and contained the estrogenic hormone in a concentration of 20,000 rat units per liter.

*These were done in the Department of Zoology through the courtesy of Professor Emil Witschi.



Fig. 2.—Biopsy of vaginal epithelium showing thickening, cornification, and papillated basal layer.

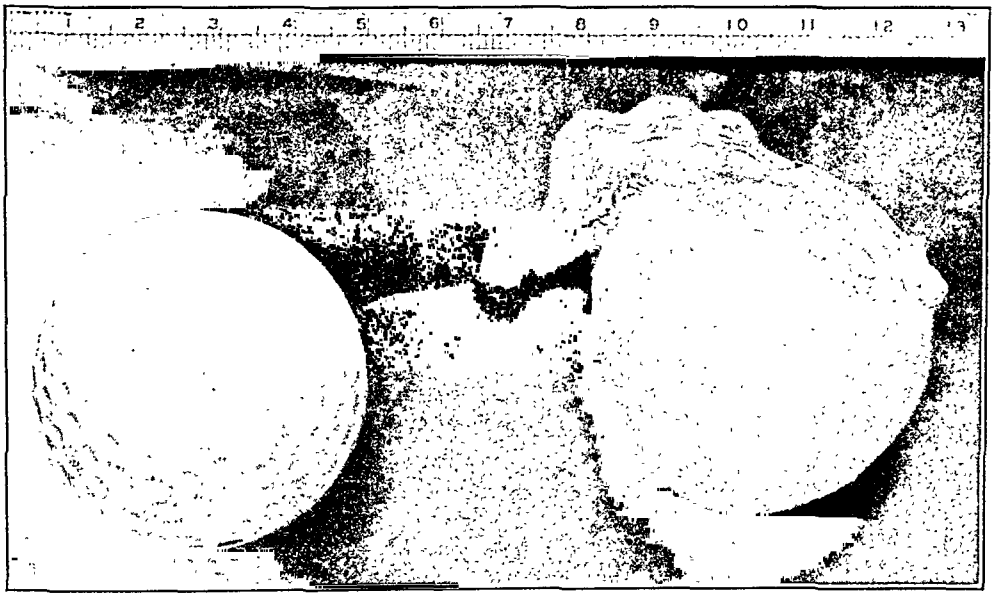


Fig. 3.—Mass removed at operation, contrasted with a golf ball. Note the adult characteristics of the Fallopian tube.

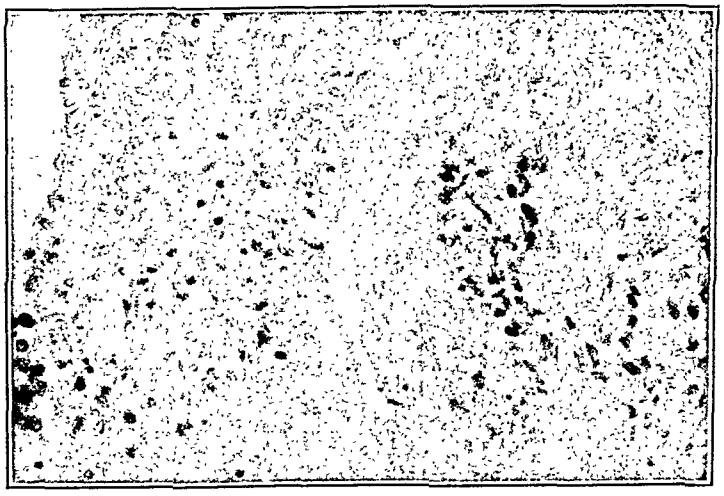


Fig. 4.—Section of cyst wall.

Neither the urine specimen obtained during the first postoperatve week, nor that obtained in January, 1938, two and one-half years after operation, gave any reaction in test rats.

DISCUSSION

Three views concerning the nature of the tumor can be entertained. It may have been: (1) a follicle cyst developing as the result of some hormonal stimulus originating elsewhere in the body; (2) a follicle cyst arising independently of any extragenital influence; (3) a primary neoplasm arising independently in the ovary.

If the tumor was a follicle cyst developing as the result of some hormonal stimulus originating elsewhere in the body, perhaps in the hypophysis or adrenal, it is difficult to credit such a stimulus with a selective action affecting only one ovary. Moreover, no tumor of hypophysis or adrenal was discovered although such a possibility was considered. Were such a tumor present, and undiscovered despite the diagnostic efforts to find it, one would have expected the child to have developed similar cysts in the remaining ovary in the three years which have elapsed since operation, and for these cysts to have given evidence of their presence by further precocious sexual development. Instead the patient has had a completely normal physical development and the breasts have regressed noticeably in size. (Fig. 1, *B* and *C*).

Follicle cysts apparently may arise independently of any extragenital influence, and Adair and Watts[1] have shown that the fluid may contain relatively high concentrations of the estrogenic hormone. However, such cystic development in a five-year-old girl is rare and difficult to understand.

The view that the cyst was a primary neoplasm is open to the objection that it contained no cells suggesting such origin. As Doctor Smith points out, ". . . ordinarily cysts of this type are not regarded as being neoplastic."

At any rate, there seems to be little doubt that this tumor was *not malignant*. Whatever its origin and its nature these basic facts remain: (1) there was sufficient estrogenic hormone in a unilateral ovarian cyst to account for precocious puberty in a five-year-old girl; (2) the premature sexual development ceased abruptly with the removal of the cyst; (3) the child has remained well and normal over a three-year period since extirpation of the cyst.

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Jacoby, Wishengrad, and Koopman: An Evaluation of the Complement Fixation Test for Gonorrhea, Am. J. Syph., Gonor. & Ven. 22: 32, 1938.

The authors state that a total of 760 patients were examined by complement fixation for gonorrhea by two different techniques with agreement in 81 per cent of the examinations. This group consisted of cases under treatment and cases for diagnosis.

In the first group, 80 per cent had positive tests. In the second group 38.5 per cent had positive tests.

In the first group the greatest number of positive tests were present in patients having gonorrhea with complications, and those in whom the disease had been present for a period of from one to six months.

A large percentage of positive tests were found in patients with acute infections and in those in whom the infection had been present less than three weeks.

In the group of patients for diagnosis, from 13.4 to 15.5 per cent showed nonspecific positive reactions.

The complement fixation test for gonorrhea has but a limited usefulness and is not reliable for diagnostic purposes. With further refinement and standardization of the technique, the test may eventually become more specific.

C. O. Maland

RUPTURE OF URINARY BLADDER COMPLICATING EARLY PREGNANCY

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IT HAS long been known that a gradually increasing obstruction of the urethra may be caused by a retroverted pregnant uterus. Such an obstruction is relieved either by replacement of the uterus spontaneously or by manipulative means, or goes on to complete obstruction with the retention of large amounts of urine in the bladder as the growing uterus becomes incarcerated in the pelvic cavity. The following case is reported because, in addition to the retention of urine, the unusual complication of rupture of the bladder was present.

Mrs. E. C., aged 38, gravida ii, para i. Wassermann negative. Date of last menstrual period, Dec. 19, 1937. Expected date of confinement, Sept. 26, 1938.

The patient was admitted to the hospital at 10:30 P.M. on March 12, 1938, complaining of severe suprapubic pain of about one hour's duration, which began following an attempt at intercourse. Actual penetration did not occur, the weight of her husband causing a sudden onset of pain in the region of the bladder. She stated that she had experienced difficulty in voiding for several weeks prior to the present illness, at times passing very small amounts of urine, at other times large amounts and, occasionally, not being able to pass any. During this time she had a sense of discomfort in the region of her bladder, apparently not severe enough for her to seek medical advice. For several days prior to the onset of the present illness, the patient stated that she had been able to void very small quantities of urine at longer intervals. She noticed that her abdomen was gradually increasing in size.

The patient was in a state of moderate shock, her color somewhat cyanotic and her respirations increased. Her abdomen was the size of a seven to eight months' pregnancy. There was marked tenderness over the entire abdomen, more marked over the suprapubic region in the midline. Involuntary spasm and rigidity were present over the entire abdomen, more marked over the lower half. Shifting dullness was elicited. The blood pressure was 108/75, the red blood count was 3.4 million, the white blood count was 27,750 and the hemoglobin was 88 per cent. On catheterization six ounces of bloody urine were obtained.

There was no evidence of trauma around the urethra or in the vagina. An old laceration of the perineum with extensive rectocele was present. The anterior vaginal wall gave excellent support. The cervix was firm, closed, slightly hypertrophied and pushed forward and up behind the symphysis. The uterus was completely retroverted, enlarged to the size of a three and a half months' pregnancy and firm in consistency. It was not movable.

A diagnosis was made of intraperitoneal rupture of the urinary bladder. The patient was given an infusion of 2,000 c.c. of saline and prepared for an immediate laparotomy. During this time signs of shock had progressed; the patient was more cyanotic, respirations more rapid, pulse 144, weak and of poor quality. Another attempt was made to catheterize the patient before operation, and 800 c.c. of bloody urine were obtained.

Under cyclopropane anesthesia, the abdomen was opened through a suprapubic midline incision. On opening the peritoneum there was a gush of bloody fluid of uriniferous odor. It was possible to measure 4,500 c.c. of this fluid, and the estimated total fluid in the peritoneal cavity was over 6,000 c.c. The bladder was collapsed, the wall being markedly thickened. In the center of the superior portion of the posterior wall, there was an irregular rupture measuring approximately 4 cm. in diameter, the edges of which bled slightly. The opening in the bladder was repaired by three inverting rows of sutures, using number 0 chromic catgut. This was ac-

complished with some difficulty because of the friability of the bladder musculature. Inspection of the pelvis revealed an enlarged uterus, the size of a three to four months' pregnancy, completely retroverted. No other abnormalities were noted. A cigarette drain was placed deep in the pelvis behind the bladder, and a rubber dam drain was inserted in the space of Retzius. The abdomen was then closed in layers. A retention catheter was inserted in the bladder. Immediately following the operation the patient was given a transfusion of 750 c.c. of whole blood.

The postoperative condition was good. Blood pressure 110/70. The course was quite uneventful. On the first postoperative day there was some cyanosis; respirations were 26 per minute. The urine output was over 1,000 c.c. in the first twenty-four hours and remained satisfactory thereafter. The abdomen remained soft, and at no time was there any distention. The wound healed by primary union. The drain in the space of Retzius was removed on the third postoperative day, and the pelvic drain taken out on the sixth. The indwelling catheter was removed on the eleventh day. Following the removal of the indwelling catheter, the patient was

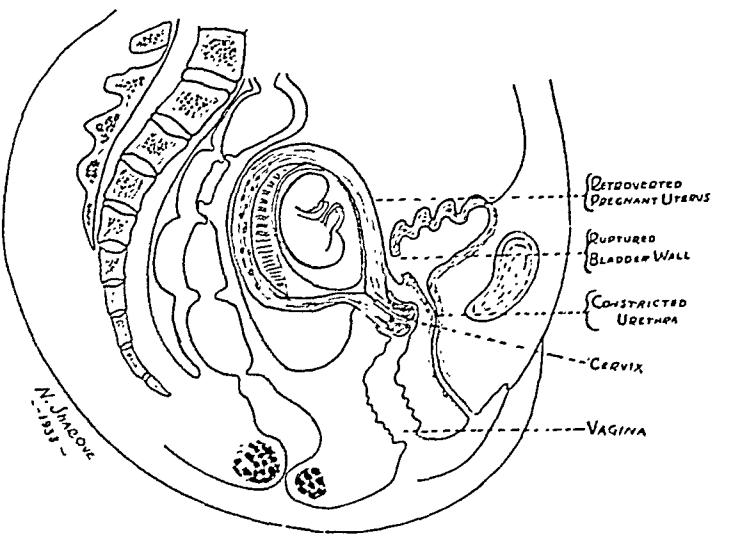


Fig. 1.—The left half of the pelvis with corresponding half sections of the bladder, cervix, uterus and rectum. The pregnant uterus is seen retroverted, and the cervix is shown obstructing the urethra. The approximate site of rupture in the posterior wall of the bladder is shown.

catheterized after each voiding and 600 to 800 c.c. of urine obtained each time. An attempt was made to increase the contractility of the bladder by administration of an ampoule of pituitrin every eight hours for four doses and an ampoule of pitocin every eight hours for four more doses without any improvement.

A neurologic examination of the patient showed no evidence of a spinal cord lesion.

On the first postoperative day, the patient aborted spontaneously a three and a half months' fetus, and three days later expelled a foul smelling placenta and membranes intact.

The patient was cystoscoped on the nineteenth postoperative day, the bladder appearing well healed. No other lesions were noted on this examination. The amount of residual urine gradually decreased to 300 or 400 c.c. The patient was not able to empty her bladder completely, even when up and about.

On the twenty-seventh day, she developed an acute follicular tonsillitis and was transferred to the Ear, Nose and Throat Service. She made an uneventful recovery and was discharged on April 12, the thirtieth postoperative day.

May 3, 1938. Since her discharge from the hospital, the patient has been feeling well. She voided three or four times daily, in fairly large amounts, and usually once during the night. She complained of no urinary symptoms. The abdominal wound was found to be well healed. On pelvic examination a moderately large rectocele was found to be present. The anterior vaginal wall showed fairly good support.

The cervix was hypertrophied, smooth, and pointed up and behind the symphysis. The uterus was normal in size, partly retroverted, and movable. After voiding, 400 c.c. of urine were obtained on catheterization.

June 27, 1938. The patient stated that she felt well and had no complaints. No urinary symptoms were present. She was voiding normal quantities of urine three to four times daily, and occasionally during the night. The pelvic examination was the same as on previous examination. The cervix was behind the symphysis, the uterus partly retroverted. She voided 500 c.c., and upon being catheterized immediately after voiding, 270 c.c. of urine were obtained. The uterus was replaced and a No. 4 pessary inserted.

July 1, 1938. The patient had no complaints. On examination, with the pessary in place, the cervix was found to be directed posteriorly and the uterus was in fairly good position although not completely anterior. She voided 580 c.c. and a residual of 160 c.c. was obtained on catheterization, immediately after voiding. At this visit the uterus was brought up in better position and a No. 5 pessary inserted.

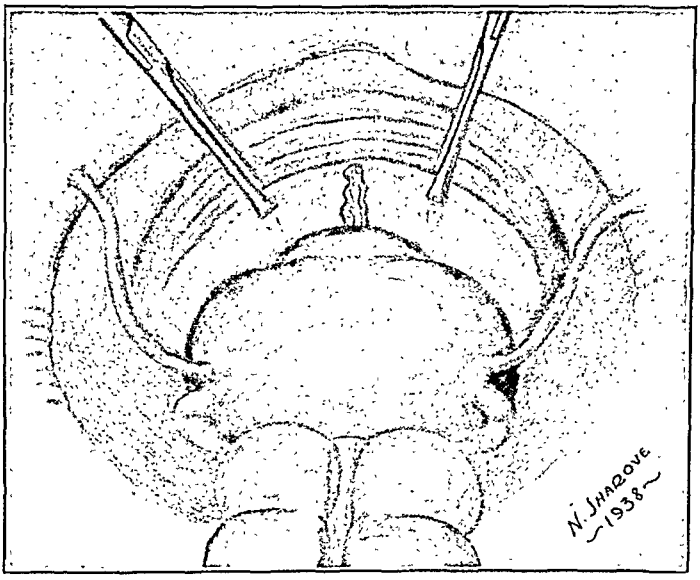


Fig. 2.—Direct view looking into the pelvis at operation, showing retroverted incarcerated uterus. The bladder is held up to show rupture in the posterior wall.

July 8, 1938. The patient had no complaints. She stated she voided more often in smaller amounts, four to five times daily and once during the night. On examination the uterus was in excellent position with the cervix away from the urethra. On this visit, the patient voided 150 c.c. and 55 c.c. were obtained on catheterization immediately after voiding. The pessary was removed and not reinserted, although the uterus and the cervix resumed their original position.

Summary.—A case is described in which rupture of the bladder occurred following an attempt at intercourse. The patient's history suggests a gradually increasing urethral obstruction due to a retroverted three and a half months' pregnant uterus which had become incarcerated in the pelvis. This had eventually resulted in the retention of large amounts of urine in the bladder. Because of distention of the bladder and consequent thinning of its wall, rupture occurred with relatively slight external trauma. Of special interest is the effect of this process on the bladder mechanism. Due, probably, to prolonged distention, the normal tone of the bladder was lost, resulting in the presence of large amounts of residual urine, not affected by treatment. Gradually the bladder regained tone, resulting in a progressively decreasing residual urine. It is not believed that the correction of the uterine displacement influenced this process.

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ESTROGENIC HORMONE IN THE URINE AND TUMOR OF A PATIENT WITH A GRANULOSA CELL TUMOR OF THE OVARY*

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THE estrogenic hormone determinations reported here were obtained from the study of a 19-year-old, single, Jewish female.† Her chief complaint was constant vaginal bleeding for more than a year. A firm left-sided freely movable adnexal tumor the size of an orange could be palpated pelvically. Complete twenty-four-hour urine specimens were obtained twice before operation, daily for ten days following operation, and at weekly intervals for five weeks following her discharge from the hospital. In addition to the urine, specimens of blood, tumor tissue, and ovarian cyst fluid were obtained for study on the day of operation. The vitamin C content of the tumor has been determined.[1]

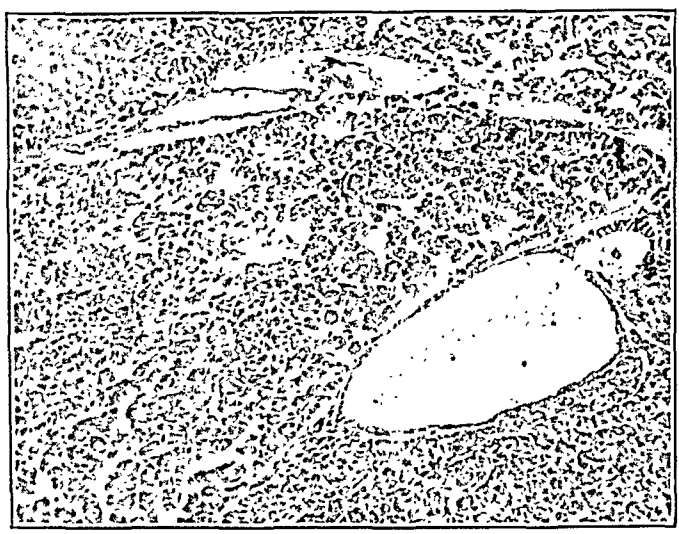


FIG. 1.—Granulosa cell tumor of the ovary. Photomicrograph of solid cellular portion of tumor used for bio-assay. (×100.)

Gonadotropic Hormone.—A quantity of each twenty-four-hour specimen was concentrated after the benzoic acid precipitation procedure of Katzman and Doisy.[2] None of the specimens of urine, obtained before or after the operation, was found to contain any active principle that showed its effect by activation of the ovaries of immature female mice. The blood, tumor tissue, and ovarian cyst fluid were not tested for gonadotropic hormone. The Friedman pregnancy test was negative.

Estrogenic Hormone.—It seems advisable to restate that in the assay of unknown estrogenic hormones by a biologic method, the result must be in terms of an estrogenic equivalent, inasmuch as the biologic method cannot be specific for one type of estrogen unless the chemical identity of that hormone is known.‡ All values for estrogenic hormone computed for this patient are equivalent to the estrogenic activity of crystalline estrone.

*This study made possible by a grant from the Christine Breon Fund for Medical Research in the University of California.

†Miss R. F., a private patient of Dr. D. A. Susnow. The pathological and clinical aspects of the case are to be reported by Dr. G. Y. Rusk and Dr. R. Rypins.

‡The ability of very small amounts of urine, obtained from this patient before operation, to produce premature vaginal opening and estrus in immature female mice, in the absence of ovarian stimulation, indicates that possibly the chief estrogen excreted was estriol.

Each extract for assay was prepared so as to obtain total estrogenic hormone content by acid hydrolysis of the urine at pH 1. The details of the method used have been outlined elsewhere.[3] The possible importance of determining the "free" and "combined" estrogenic hormone proportions was not fully realized at the time extracts were prepared; but a parallel assay procedure carried out on one specimen preoperatively, using whole urine, indicates that the urinary estrin was excreted almost entirely in its "free" state. The test animals used throughout were controlled according to a plan already described.[4]

The estrin content of the blood serum and ovarian cyst fluid was apparently much less than anticipated and consequently was not demonstrated in the amounts of these fluids tested. The estrin content of the tumor was obtained by finding the smallest amount of fresh tumor tissue which, implanted into the peritoneal cavity of

TABLE I. ESTROGENIC HORMONE EXCRETED BY PATIENT BEFORE AND AFTER OPERATION

DATE	URINE SPECIMEN	ASSAY (ESTRONE EQUIVALENT)
10/ 7/35	Preop. 16 weeks	40.0 gamma/24 hours
10/24/35	Preop. 13½ weeks	66.6 gamma/24 hours
1/27/36	Day of operation	86.6 gamma/24 hours
1/28/36	Postop. 1 day	10.0 gamma/24 hours
1/29/36	(Incomplete spec.)	
1/30/36	Postop. 3 days	20.0 gamma/24 hours
1/31/36	Postop. 4 days	8.0 gamma/24 hours
2/ 1/36	Postop. 5 days	6.6 gamma/24 hours
2/ 2/36	(Incomplete spec.)	
2/ 3/36	Postop. 7 days	0.0 gamma/24 hours
2/ 4/36	Postop. 8 days	2.5 gamma/24 hours
2/ 5/36	(Incomplete spec.)	
2/ 6/36	(Incomplete spec.)	
2/ 7/36	Postop. 11 days	4.6 gamma/24 hours
2/20/36	Postop. 3 weeks	11.0 gamma/24 hours
2/27/36	Postop. 4 weeks	0.0 gamma/24 hours
3/11/36	Postop. 6 weeks	0.0 gamma/24 hours
3/18/36	Postop. 7 weeks	13.0 gamma/24 hours
3/25/36	Postop. 8 weeks	4.0 gamma/24 hours
1/27/36	Blood serum	less than 50.0 gamma/liter
	Ovarian cyst fluid	less than 50.0 gamma/liter
	Tumor tissue (desiccated)	11,700.0 gamma/kilogram

TABLE II. QUANTITATIVE ASSAY OF ESTROGENIC HORMONE IN RECORDED CASES OF GRANULOSA CELL TUMOR

AUTHOR	URINE ESTRIN	TISSUE ESTRIN	
		FRESH	DESICCATED
1930 Schuschania[5]	65 M.U./liter	47 M.U./kg.	
1933 Dworzak[6]	50 M.U./liter (postop.)		
1935 Bland[7]	300 M.U./liter		
1935 Geist[8]		1,000 M.U./kg.	
1935 Geist (Thecoma)[9]		1,500 M.U./kg.	
1935 Szathmary[10]	360 M.U./liter (postop.)		
1935 Thornton[11]	7½ M.U./liter (postop.)		
1936 Gospe[12]		3,200 M.U./kg.	36,000 M.U./kg.
1937 Studdiford[13]	8 R.U./liter (postop).		
1937 Anderson[14]	17,390 M.U./liter	5,000 M.U./kg.	
1937 Meigs[15]		530 M.U./kg.	
1938 Palmer (this case)	866 I.U./liter (Calculated as estrone)	20,000 I.U./kg. (Calculated as estrone)	117,000 I.U./kg.

a controlled test mouse, would produce complete vaginal cornification in that animal. The value for desiccated tissue was calculated from that for fresh tissue.

The values for tissue estrin in this case, although higher than others taken from the literature, is conservative, as all such values must be. As yet it has not been possible to prepare a medium containing a known amount of crystalline estrone, for purposes of abdominal tissue implant procedures, that would be similar in every respect to the hormone in tissue cells elaborating that hormone. In a separate experiment an attempt was made to simulate slow continued peritoneal absorption of estrogenic hormone as might occur from a mass of fresh tissue cells, by injecting known amounts of estrone in olive oil solution intraperitoneally into 100 newly castrated mice. This experiment was temporarily abandoned when it was found that not one of the 100 mice developed full vaginal cornification after the intraperitoneal administration of ten times the cornifying subcutaneous dose of the same oily solution.

DISCUSSION

The amount of estrogenic hormone excreted daily by this patient before operation, while approximately 4 to 5 times the average daily excretion by a normal nonpregnant woman, is about equal to the amount excreted daily by a woman six to eight weeks pregnant. A normal woman may excrete more estrogenic hormone in a single twenty-four-hour period during the peak of hormone excretion, i.e., the midintermenstruum than was excreted daily by this patient with the granulosa cell tumor. However, the point of difference is that this patient was bleeding while excreting the hormone. When a normal woman menstruates, her estrogenic hormone excretion is at its lowest. Usually the amount is not demonstrable.

If a reason needs to be given for a tumor so rich in estrogenic hormone content being associated with only moderately increased excretion of hormone, it may be conjectured that the continuous vaginal bleeding which this patient endured possibly accounted for the greatest loss of estrogenic hormone from her body. Reference to this possible means of excretion associated with fall in kidney excretion of hormone has been made previously.[3, 16] It is interesting to note also that the only case reported in Table II associated with a tremendous hormone excretion was one of granulosa cell tumor in a child of four who had had no vaginal bleeding. Anderson's patient[14] continued to excrete an excessive amount of estrogen two days after operation, and it was not until some time after the first vaginal bleeding occurring on the third postoperative day, that his patient was excreting normal amounts of hormone. On the other hand, in my report the excretion of estrogenic hormone was normal beginning the first postoperative day and thereafter.

SUMMARY

Estrogenic hormone determinations on the tumor and urine of a patient with a granulosa cell tumor of the ovary are reported. Values for the hormone are calculated as estrone. The content of the tumor was found to be 11,700.0 gamma (11.7 mg.) per kilogram desiccated tumor tissue associated with a maximum urinary excretion of 86.6 gamma per twenty-four hours while the patient was bleeding. Beginning the first day after operation the urinary excretion of estrogenic hormone fell to normal. Comparable values from other cases recorded in the literature are tabulated.

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A NEW, NONIRRITATING OPAQUE MEDIUM FOR UTEROSALPINGOGRAPHY

II. Elimination of Acacia

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THE use of iodized oils in the x-ray visualization of the uterus and Fallopian tubes is occasionally followed by troublesome reactions. Following its injection, acute "chemical" salpingitis, parametritic masses, and occasional allergic reactions have been reported. It has recently been shown by our group[1, 2] that a solution of mono-iodomethane sulphonate of sodium (skiodan) with acacia is a nonirritating medium for uterosalpingography. Skiodan is not irritating to the uterus and tubes. It is rapidly eliminated from the body through the urine and does not liberate free or inorganic iodine.

These studies did not show, however, the effect of the acacia used as a vehicle nor whether the acacia was eliminated. That a knowledge of the effect and fate of acacia is important is pointed out in the literature by several investigators[3-5] who have shown that acacia when injected in large doses intravenously causes damage to the liver. Others[6] express the clinical view, however, that, "long continued presence of acacia within the body without apparent harmful effects demonstrates anew its innocuous character in man." We wished to be certain, in addition, that the acacia would not become encysted in the peritoneal cavity, as is so often the case with iodized oil injected for uterosalpingography.

To complete the study of the effect of, and the fate of, skiodan-acacia, a series of experiments was devised to study the action of the acacia upon the uterus, tubes, and peritoneum, if any, and to determine its fate upon injection into the female internal genitalia and the peritoneum.[1]

SUMMARY OF EXPERIMENTS

Our experiments with acacia fall into three parts; first, a determination of the local or general effect of the injection of acacia into the genitalia and peritoneum of female rabbits, second, a study of the blood and urine thereafter for acacia, and third, chemical and microscopic studies of the livers of rabbits so injected.

1. Local and General Effects

Three rabbits were injected with varying amounts of acacia in different ways. Rabbit 101 received 2 c.c. of 20 per cent acacia in the uterus and tubes following the technique used in our preceding experiments.[2] There was no immediate reaction of any kind. After thirty-two days this rabbit was killed and the peritoneum and internal genitalia carefully examined. There was no evidence of the acacia in the peritoneum or genitalia, nor was there any evidence of inflammation or irritation. The liver was examined and found grossly to be normal. Rabbit 102 received 5 c.c. of

20 per cent acacia directly into the peritoneum. There was no immediate reaction and after twenty-five days this rabbit was killed. The gross examination of peritoneum and liver did not show any evidence of irritative effect. Rabbit 103 received 6.6 c.c. of 30 per cent acacia directly into the peritoneum and was killed seven days afterward. In this instance the fluid in the peritoneum contained less than 0.1 mg. of acacia per c.c. with no evidence of irritation, encysting of this substance in the peritoneum, or damage to the liver.

2. Chemical Tests for Acacia in Blood and Urine

There is no specific test for acacia. For studies of acacia in urine Sumner's method[7] is not effective since acacia does not reduce Sumner's reagent. Normal urine contains materials that produce furfural upon treatment with acid so that a test by the method of Youngberg[8] must be a differential one. Bial's orcinol-hydrochloric acid reaction for pentose in urine is perhaps the best indication of the presence of acacia in urine.



A. *B.* *C.*

Fig. 1.—*A*, Rabbit 101 liver thirty-two days after injection of 0.4 gm. of acacia; *B*, Rabbit 102 liver twenty-five days after injection of 1.0 gm. of acacia; *C*, Rabbit 103 liver seven days after injection of 2.0 gm. of acacia.

It was found (see Table I) that minute amounts of acacia could be detected in the urine at intervals of from 6 to 108 hours after injection. It was concluded that if acacia is excreted in the urine it must be in only small amounts and perhaps over a very long period of time as was found by Andersch and Gibson.[3]

For studies of acacia in the blood the oxidimetric method of Keith, Power and Wakefield[6, 9] was employed, using 95 per cent ethyl alcohol as the precipitating agent. In the first two rabbits we were disappointed not to find the suspected large amounts of acacia in the blood but upon reading the work of Putnam[10] we realized that we were not sampling the blood early enough to pick up the higher levels of the acacia (see Table I). Rabbit 103 showed that the level of acacia reached a maximum at about six hours after injection and rapidly fell to approximately normal in less than seventy-two hours.

3. Chemical and Microscopic Studies of Livers

Several investigators[3-5] have pointed out that the liver is damaged following intravenous use of relatively large amounts of acacia. We felt that we must know if acacia injected into the female internal genitals and peritoneum in the recommended dosage would have a like effect. Rabbits were injected with amounts corresponding to 4 to 20 times the amounts usually used in the human being for uterosalpingography. These rabbits were killed at thirty-two, twenty-five, and

TABLE I. DETERMINATION OF ACACIA IN BLOOD AND URINE

RABBIT	ACACIA INJECTED	URINE		BLOOD	
		TIME AFTER INJECTION	ACACIA BIAL'S TEST	TIME AFTER INJECTION	ACACIA IN BLOOD SERUM
101	0.4 gm.	12 hr.	None	36 hr.	208.0 mg./100 c.c.
		36 hr.	Trace		
		60 hr.	None		
		84 hr.	Trace		
		108 hr.	Trace	84 hr.	13.1 mg./100 c.c.
102	1.0 gm.	12 hr.	Trace	48 hr.	18.0 mg./100 c.c.
		36 hr.	None		
		42 hr.	None		
		62 hr.	Trace	96 hr.	30.3 mg./100 c.c.
103	2.0 gm.	6 hr.	None	3 hr.	316.0 mg./100 c.c.
		24 hr.	None	6 hr.	476.0 mg./100 c.c.
		72 hr.	Trace	24 hr.	312.0 mg./100 c.c.
				72 hr.	4.0 mg./100 c.c.

TABLE II. DETERMINATION OF ACACIA IN LIVER

RABBIT NO.	ACACIA INJECTED	TIME AFTER INJECTION	ACACIA IN LIVER	MICROSCOPIC SECTION LIVER
101	0.4 gm.	32 days	29.9 mg./gm.	Normal
102	1.9 gm.	25 days	23.5 mg./gm.	Normal
103	2.0 gm.	7 days	25.4 mg./gm.	Normal

seven days after injection of acacia. In Rabbit 101 the injection was made into the uterus and tubes while in the remaining two rabbits the acacia was placed directly into the peritoneum. The livers were examined in situ in the gross and were found to present a normal appearance as to shape, size, margins, and surfaces. They were immediately removed from the body and a portion placed in Zenker's fixative for microscopic study and a second portion taken for quantitative estimation of the amount of acacia therein. For this analysis the method of Youngberg[8] as used by Andersch and Gibson[3] was employed. The amount of furfural producing material, calculated as acacia, in all three livers was just above that given by Andersch and Gibson[3] as normal (Table II).

The microscopic study of these livers did not show the destruction and swelling of liver parenchyma as found by others following intravenous injection of larger amounts of acacia,[3-5] and it was felt that all sections represent essentially normal histology.

SUMMARY

1. Experimental data indicate that acacia injected in the amounts used in uterosalpingography does not irritate the internal genitalia or peritoneum in rabbits.

2. Acacia does not remain in the peritoneum but is rapidly taken up and appears in the blood stream within three hours following its injection. The maximum level of acacia in the blood is reached within six hours, and it has almost disappeared from the blood in seventy-two hours.

3. We could not prove that acacia is excreted in the urine. It has been shown by Andersch and Gibson that in bile fistula dogs, acacia appears within six hours in the bile, and it is most likely that the bile is the means by which it leaves the body.

4. Microscopic studies of the livers up to thirty-two days after injection of more than ten times the amount of acacia used in human uterosalpingography did not show liver damage.

5. The amount of furfural producing material, calculated as acacia, in the liver was just above that said to be normal.

CONCLUSION

Our previous findings show that skiodan produces satisfactory x-ray shadows, and further is nonirritating to the tissues and is rapidly eliminated from the body. Our present findings show that acacia is nonirritating, is not retained in the peritoneum and does not cause liver damage. We conclude that skiodan-acacia in uterosalpingography is harmless in the amounts used and is, therefore, to be preferred to the older opaque media (iodized oils).

The materials for this investigation were generously furnished by the Winthrop Chemical Co., New York.

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RELAXATION OF THE PELVIC LIGAMENTS IN PREGNANT MONKEYS

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Profound changes occur in the pubic and sacroiliac joints in many of the lower mammals during the course of gestation. The hormonal control of the tissue metamorphoses involved has been fairly well worked out.[1] An examination of modern textbooks of obstetrics[2, 3] as well as the current literature on the subject indicates that pelvic relaxation in women is generally recognized. Most of the clinical literature concerns cases of pathologic exaggeration of the process which may lead to separation of the pubic bones and consequent distressing symptoms. The pregnancy changes in the ligaments as a normal and physiologic process is also stressed or taken for granted. Thus Kehrer[2] states that the motility of the pelvic bones, by loosening of the joints, has not only a pathologic significance but above all a physiologic one; for it makes possible an increase in the diameter of the birth canal. DeLee[2] says that "in the human there is no doubt but that the joints soften, thicken and thus enlarge the cavity of the pelvis. The bones become more movable on each other. . . ."

The relaxation of the pelvic ligaments has been noted in scores of cases in the rhesus monkey (Macaca mulatta) and in six specimens

of the bonnet monkey (M. radiata) of the Carnegie monkey colony. It is the purpose of the present paper to record these facts.

METHOD OF DIAGNOSIS

The monkey possesses prominent ischial tuberosities over which the skin forms cornified pads, the "sitting pads."[4] To test the mobility of the pelvic bones, the animal is laid ventral side down across a suitable block so that the tuberosities are turned up. Each of these is grasped by a thumb and traction placed upon them. The amount of spread is measured by means of calipers and the result is recorded in millimeters. The spread of the joints, if considerable, may also be felt readily by pressing a finger into the clefts formed in the symphysial joint.

In this experiment most of the symphysial spread is caudal and very little at the cranial margin of the pubis. This is due to the rotation of the innominates and a tilting of the acetabular borders, as one would expect from a study of the parts in a prepared skeleton. The rotation may also be proved in the living animal, placed on its side, with a lever laid across the lateral margin of the innominate bone. On spreading the tuberosities the long free arm of the lever may be seen to dip by reason of a depression of the edge of the rotating innominate. This may also be regarded as evidence of relaxation in the sacroiliac joints.

In pregnant women, Abramson, Roberts and Wilson[5] could also regularly demonstrate the mobility of the pelvic bones by tactile examination. While an assistant alternately pulls on one leg and pushes on the other the examiner is able to feel, with his finger placed over the symphysis, the movements of the bones with reference to each other.

RESULTS

Nonpregnant Controls.—Some males and many nonpregnant females were tested as controls. For these animals the figures are without exception low, usually 1 or 2 mm. Some females, however, had pelves uniformly more mobile, registering differences of 3 or 4 mm. These were mostly multiparas, though some multiparas had tight joints except in pregnancy. The ligaments of males and castrated females never showed the slightest looseness. In most females the stage of the menstrual cycle made no difference; but a few females gave the impression of slight relaxation (doubling the spread) toward the end of the cycle.

Pregnant Females.—Some typical cases are the following:

Rhesus Monkey No. 51:			
	July 11, 1932,	one month before parturition	2.0 mm.
	Aug. 1,	11 days before parturition	10.0 mm.
	Aug. 12,	*parturition*	
	Aug. 13,	day after parturition	11.0 mm.
Rhesus Monkey No. 2:			
	Eighty-first day of pregnancy		4.0 mm.
	106th day of pregnancy		4.5 mm.
	At parturition 1933		16.0 mm.
Rhesus Monkey No. 173:			
	March 1, 1932,	30 days before parturition	10.0 mm.
	March 10,	10 days before parturition	12.0 mm.
	March 31,	parturition	18.0 mm.
	April 3,	4 days post partum	8.0 mm.
	April 19,	19 days post partum	3.0 mm.
Rhesus Monkey No. 236:			
	Oct. 21, 1933,	7 days before parturition	15.0 mm.
	Oct. 28,	parturition	
	Nov. 1,	3 days post partum	10.0 mm.
	Nov. 10,	13 days post partum	6.0 to 8.0 mm.
	Nov. 13,	16 days post partum	6.0 mm.
	April, 1934	many tests	3.0 to 4.0 mm.

Bonnet Monkey No. 150:

May 19, 1934,	parturition	
May 21,	2 days post partum	18.0 mm.
May 25,	6 days post partum	16.0 mm.
May 27,	8 days post partum	15.5 mm.
June 22,	one month post partum	2.5 mm.

Monkey No. 36 is of especial interest. On June 30, 1930, she was hypophysectomized, but her subsequent history showed that some pituitary substance was retained. After a long period of amenorrhea she again menstruated and ovulated. On April 18, 1932, she gave birth to a baby. *Six days and 2 days before parturition* the relaxation figures stood at only 5-6, but at the time of parturition the figures were 11-13 and the following day 16 mm. No explanation is offered for this anomalous behavior.

Relaxation is not usually much advanced before the last month of gestation, which in the monkey has a duration of six lunar months (against 10 for the human being). In women relaxation is said to begin in the fourth month, which in absolute time approaches the beginning of relaxation in the monkey. The post-partum reversion to the normal, firm, nonpregnant condition is accomplished within three or four weeks.

Castration during pregnancy in no wise interferes with the loosening of the pelvic ligaments. Nor is a living fetus necessary, for several cases of complete relaxation were noted after the delivery of a dead, even macerated, fetus near term.

The histologic changes in the ligaments are not great, although no exhaustive study of the problem was made. There seems to be no indication of bone growth such as described by Loeschcka[6] for women, nor is there any bone resorption or transformation of the connective tissue as described for some of the lower mammals. The only change which a section of the symphysis of a pregnant animal showed when compared with the control was a loosening of the connective tissue fibers due apparently to an edema of the tissue. Whether or not this was preceded by formation of new elements by cell multiplication remains an open question.

SUMMARY

Relaxation of the pelvic ligaments is an invariable accompaniment of pregnancy in the rhesus and the bonnet monkeys. The condition becomes manifest in the last of the five and one-half months' gestation period and reverts to the nonpregnant condition of firmness within three or four weeks after delivery. The changes take place despite castration early in pregnancy or death of the fetus. The loosened ligaments are characterized by edema.

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EUTOCIA COMPLICATED BY LYMPHOPATHIA VENEREA, PERIRECTOANAL MASS, AND RECTAL STRICTURE

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RECENTLY Michelson, Crotty and Kasselberg reported the first proved case of lymphopathia venerea with esthiomene associated with pregnancy.[1] Similar cases were reported by Wilson, in 1930; Das, in 1931; and Gaines and McDowell,[2] in 1936, but these were not confirmed by the Frei test, which is now regarded as determinative in diagnosis of 97 per cent of all cases. Of two cases reported by Dick[3] in Germany, one had been diagnosed only on the clinical picture; the other had a positive Frei test. The latter had a rectal stricture but, like the case reported in this paper, Dick's patient did not have esthiomene of labia majora.

We wish to report one additional case in a pregnant colored woman, with rectal stricture and with a perianal mass, 8 by 4 cm., and hypertrophy of both labia majora, who from a positive Frei skin test was diagnosed as having lymphopathia venerea. She gave birth to a normal infant; the latter, like the child in Michelson's report, but unlike the two children reported by Dick, failed to show a positive Frei test.

CASE REPORT

Mrs. L. F., aged 35, grav. vi, para iv, colored, widow, was first admitted to the University of Nebraska dispensary in 1935 with a complaint of a mass about the anus for some ten years. Blood Wassermann was 4-plus and she was put on antisyphilitic treatment.

In November, 1936, she complained considerably about loose stools and pain in the region of the rectum during defecation and was at that time found to have a positive Frei test. She was treated by antimony and bismuth with some relief of her symptoms. Since that time she has been found to have a positive Frei test on numerous occasions, two different antigens having been used for this purpose.

In October, 1937, she entered the prenatal clinic complaining of an amenorrhea since June, 1937, and was found to be about four months pregnant.

Significant past illness: Gonorrhea and syphilis. In spite of the fact that she has had difficulty with a perirectoanal mass and a stricture of the rectum for some ten years, her obstetric history is significant because of the absence of dystocia caused by rectal stricture.

In 1921 she had an inevitable abortion; in 1923 a living baby girl, short labor; in 1925 a living baby girl, in labor for only one hour; in 1928 a living baby boy, in labor one hour; in 1930 a living baby boy, with a very short labor.

On Jan. 30, 1938, when about seven months pregnant, she was admitted to the University Hospital complaining of severe abdominal pain, numerous loose stools and chills accompanied by a temperature of 102° F. The diarrhea was controlled by paregoric and bismuth and as the patient was not in labor, she was sent home. Following this, she was seen on numerous occasions by the outpatient department for similar attacks of diarrhea until she was readmitted to the hospital March 8, 1938, complaining of chills and fever. Examination revealed the patient at term with a rectal stricture which would not permit of digital examination and a perirectoanal mass about 8 cm. in length by 4 cm. in width, located at the left and somewhat inferior to the anus and a hypertrophy of the labia majora (Fig. 1).

Laboratory Findings.—A catheterized specimen of urine showed 200 W.B.C. per high power field. Hemoglobin 52 per cent, R.B.C. 3,570,000, W.B.C. 10,150, segmented 61 per cent, staff 9 per cent, lymphocytes 26 per cent, monocytes 4 per cent.

Blood Wassermann as well as Kahn tests was negative. The sedimentation rate was 24 mm. in twenty-two minutes.

Blood chemistry: Serum nonprotein nitrogen 23.4 mg. per cent, total serum protein 7.6 per cent, serum albumin 3.8 per cent, serum globulin 3.8 per cent, fibrogen 0.4 per cent. Blood pressure 110/72.

Course in the Hospital.—At time of admission, the patient was apparently suffering from a pyelitis which cleared immediately following delivery. She went into labor on the fourth day following admission and delivered normally, after three and one-half hours of labor, a living female child, weighing 7.5 pounds. A first degree laceration was sustained but of not enough moment to require suturing. A very normal puerperal course followed and the patient was dismissed on the tenth post-partum day. Since then, she has reported to the dispensary and her Wassermann reaction was reported as 1-plus, while both the Kline and Kahn reactions were negative. At present she is again receiving antisyphilitic treatment. The baby's Frei test was negative on the fifth post-partum day and again negative when the child was four months old.



Fig. 1.

DISCUSSION

This case of a colored patient is very similar to the one, also colored, reported by Michelson, Crotty, and Kasselberg with the exception that our case was complicated by perirectoanal mass instead of esthiomene. In our patient's case, the syphilitic background is of comparatively little interest, as in the case reported by Michelson and others. Many investigators report concomitant syphilis in patients with lymphopathia venerea. The clinical and laboratory findings show the patient to have had a chronic condition of lymphopathia venerea during the course of which she successfully gave birth to a normal full term child. Gaines and McDowell,[2] who report a fatal case of delivery of a woman with a severe rectal stricture due to rupture of the rectum, recommend cesarean section in all such cases. In our patient, no such difficulty with rupture was encountered. Apparently from her former history, since having a perirectoanal mass as complication, she has delivered two other normal living children prior to this time without any harm to either patient or children.

Although changes in the genitalia had not progressed so far that elephantiasis or esthiomene could be diagnosed, yet there was an additional perirectoanal growth

previously described, in addition to hypertrophy of labia majora. The effect of the lymphopathia venerea on fertility is still problematical. Michelson and others, besides reporting the one case, cite only Dick. The latter states, categorically, that females in the late stages of the disease are sterile or unable to find sexual partners; but he gives no proof of sterility nor does he offer explanation for the etiology.

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ENDOMETRIOSIS OF THE UMBILICUS

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(From the Gynecological Department of The Barnard Free Skin and Cancer Hospital)

Extrapelvic location of endometrial tissue is uncommon. The umbilicus is one of the rarer locations of endometriosis. Strongin states that only a total of 68 cases have been reported in the entire world until the end of 1935.

I. L., a 40-year-old white, married female, was seen in the Gynecological Clinic of The Barnard Free Skin and Cancer Hospital on Jan. 24, 1938, complaining of abdominal pain and pain in the umbilicus, before, during, and after each menstrual period. This condition was present since the onset of her menstrual cycle, the sequence of symptoms being the same with each menstrual period. The pain started four to five days before each period, continued throughout the period, and persisted for four to five days after its cessation. The umbilicus became quite tender during this time and assumed a bluish discoloration. There was no evidence of external bleeding. Menses began at the age of eleven and appeared every twenty-eight days, and lasted five days. The patient complained of dysmenorrhea and menorrhagia. She had two pregnancies with two normal, full-term deliveries.

The patient had painful breasts with each menstrual period. Two nodules were found in the right breast, both of which were removed, and on pathologic examination proved to be intracanalicular fibroadenomas.

On examination the cervix appeared normal. The corpus was in second degree retrodisplacement, enlarged, freely movable, tender, moderately softened. (Patient examined during premenstrual phase.) There were no adnexal masses or tenderness. The umbilicus was tender, firm, and showed a faint bluish discoloration. No umbilical mass or hernia was present.

The clinical diagnosis was pelvic endometriosis and endometriosis of the umbilicus.

The patient was operated upon on Jan. 26, 1938. The uterus was found to be enlarged three times normal size and densely adherent to the small intestines. The adhesions were difficult to separate. The right ovary contained a blood-filled cyst about 2 cm. in diameter. The appendix was normal. A supravaginal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were done. The umbilicus was removed, including its underlying peritoneum.

Pathologic Examination.—The umbilicus was 2 cm. wide, surrounding a nodule 1 cm. in diameter, underlying which was a definite tumor mass 2 cm. in diameter. On cut section this tissue contained a number of cysts filled with clear material. Grossly, there was no apparent involvement of the skin. The peritoneal surface was infiltrated with several nodules of tissue, which were hard and irregular. The peritoneal surface of the mass was deeply umbilicated. There were no adhesions of any abdominal viscus to the umbilicus. The wall of the uterus at the internal os measured 3 cm. in diameter. The endometrium was 4 mm. thick, and glistening. The ovaries and appendix appeared as described above.

Microscopically, the umbilical tissue showed numerous endometrial glands, presenting evidence of secretory activity (Fig. 1). The glands varied in size and shape,



Fig. 1.



Fig. 2.

Fig. 1.—Low power section of the umbilicus, showing endometrial glands surrounded by endometrial stroma. In the lumen there is some secretion from the glands. (×130.)

Fig. 2.—Section of right ovary showing two glands surrounded by endometrial stroma. In the upper left hand corner of the section can be seen a portion of the epithelium covering the ovary. (×130.)



Fig. 3.



Fig. 4.

Fig. 3.—Section of the endometrium showing glandular hyperplasia with the glands in the premenstrual phase. (×130.)

Fig. 4.—High power magnification of Fig. 1. The epithelium of the glands is columnar and shows secretory activity. (×540.)

and were surrounded by a moderate amount of endometrial stroma. There was no microscopic evidence of any infiltration of the skin by the endometrial glands. The section also failed to reveal any involvement of the parietal peritoneum by these glands. The endometrium was hyperplastic (Fig. 3), the state of activity of the glands being similar to that found in the umbilical endometrioma. The wall of the uterus was thickened, due to subinvolution and hypertrophy. The right ovary showed several endometrial glands near its surface (Fig. 2).

INTRALIGAMENTOUS, PAROVARIAN CYST

MANLY E. HUTCHINSON, M.D., COLUMBIA, S. C.

ALTHOUGH many instances of very large abdominal tumors have been reported in medical literature, I have not been able to find a record of an intraligamentous, parovarian cyst approaching the size of this one, which is being reported simply as a matter of curiosity.

The patient was a colored woman, thirty-eight years of age, admitted to the Gynecological Service of the Columbia Hospital Feb. 14, 1938. The chief complaint was inconvenience due to her enormously enlarged abdomen. There was no dyspnea while lying quietly in bed, and no edema of lower extremities. The abdominal tumor was noticed first about ten years ago, soon after the delivery of twins, and had gradually increased in size. There had been 11 pregnancies and 11 full-term labors, 4 of these having occurred since the tumor was first detected. Menstruation had always been regular and otherwise normal.

The patient weighed 164 pounds and was 5 feet 1 and ½ inches tall. She was poorly nourished and had extensive oral sepsis. The radial arteries were hard. The blood pressure was 190 over 126. The heart and lungs were displaced upward. The abdomen was greatly distended, having a circumference of 52 inches at the navel and measuring 30 inches from the pubis to the xiphoid. There was an old drainage scar midway between the pubis and umbilicus. Dullness was present throughout and a distinct fluid wave could be elicited over any area. There was no tenderness. The pelvic examination revealed a relaxed pelvic diaphragm with marked cystocele and rectocele. There was a bloody discharge from the cervix, which was drawn high up almost out of reach against the left pelvic wall. The uterus and adnexa could not be palpated. The entire pelvis was filled with a soft, cystic mass which seemed to be pushing the uterus up and to the left.

The hemoglobin was 60 per cent (Dare). The Wassermann and Kahn reactions were negative. A catheterized specimen of urine was negative except for two-plus pus. The kidney function, as determined by the phthalein, blood urea and urea nitrogen tests, was normal.

The diagnosis was large, right ovarian cyst, probably intraligamentous; cystocele; rectocele; oral sepsis, and arteriosclerosis.

Operation was done Feb. 24, 1938. The patient was narcotized with morphine and hyoscine. The skin was infiltrated with novocaine and a small incision made in the midline below the umbilicus. There was extensive thinning of the abdominal wall, which consisted only of skin, fascia and peritoneum. The cyst wall was exposed, a medium sized trocar was inserted into the cyst and 31,000 c.c. of clear, straw-colored fluid drawn off slowly over a period of forty-five minutes. The puncture site was then clamped and tied. The patient was given nitrous oxide and oxygen and the incision extended downward. The tumor wall was adherent by fine adhesions to the anterior parietal wall. With the right horn of the uterus, it was densely adherent to an old scar about midway between the pubis and umbilicus. The cecum and appendix were displaced into the upper left abdomen. The trocar puncture was found to be through the posterior layer of the right broad ligament. The adhesions were released and the anterior layer of the right broad ligament was opened. A line of cleavage was found and the cyst wall, still containing 5,000 c.c,

of fluid, was shelled out from the posterior parietal peritoneum and broad ligament, with practically no bleeding. There was no pedicle and the right ovary was normal. The opening in the broad ligament was sutured and the abdominal wound closed.

The patient's general condition improved during the operation so that, at the end, the original hypertension and rapid pulse rate had dropped to normal. However, when the anesthetic was stopped, signs of shock occurred, but these disappeared as soon as a pillow was strapped tightly over the abdomen.



Fig. 1.

A total of 36,000 c.c., or approximately 9½ gallons, of fluid was obtained from the cyst. The inner surface of the cyst wall was smooth and glistening. The pathologic report was: Massive, serous parovarian cyst.

The patient made an uneventful recovery, was fitted with a surgical corset and dismissed about three weeks after operation. On the day of her dismissal she weighed 74 pounds less than when she was admitted. Six weeks later, she had gained 17 pounds.

A NEW OBSTETRIC PHANTOM

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THE first obstetric phantoms seem to have been constructed and used in the seventeenth century in France. At present there are available fourteen, some of which have definite imperfections. Many other phantoms (about 65) have been mentioned or described but are no longer obtainable. Phantoms like those of Stander, Jacobs or Ayers have seemed the most desirable for demonstrating certain phases of labor and especially forceps deliveries. However, in using some of the others, teachers have been compelled to show the forceps or other maneuvers outside of the phantom rather than in the pelvic cavity, because most of them will not admit of the delivery of a full-term fetus or a doll of corresponding size. Moreover, I am not concerned about reproductions of the abdominal wall or of the uterus, which can be studied safely and to better advantage in living patients. Neither am I much interested in the artificial representation of the vulvar outlet, at best an unsatisfactory makeshift. From any actual delivery one can learn more about this region. The really puzzling thing is what happens within the pelvis itself, and this one can visualize and teach more effectively with one of the three makes mentioned above.

One disadvantage of the metal pelvis has been that in using it, a good forceps may be scratched. To overcome this the Stander pelvis was wrapped with a flannel bandage and a leather doll was used instead of the metal head. Subsequently, the makers substituted for the aluminum head a rubber head and shoulders. Then the writer had the inner surface of the pelvis lined with rubber which was carried over the edges of the bones (Figs. 1 and 2). Serious thought was given to the suggestion to have the pelvic muscles represented in rubber somewhat as they are built up in the University of Oregon obstetric manikin but the idea was abandoned. A number of changes were made by the producing company or initiated by the author. The base was made smaller so that it would fit into a bag. The rod supporting the pelvis was shortened and was moved up to the very edge of the base instead of being three inches back, changes which correspond to bringing the patient's buttocks to the edge of the delivery table, a necessary move in most forceps operations.

From an extension of the spine there was carried out over the pelvic inlet a bar in which holes had been drilled. Into these holes a rod was fastened bent at an angle so that it represented the pelvic curve (Fig. 1). First a flexible copper rod was used until the curve had been determined and then a steel rod was fashioned to that exact pattern. Meanwhile an opening had been made in the top of the rubber head so that the rod could pass through it and through the hollow neck. By enlarging this opening along the sagittal suture, flexion of the head on the rod was permitted. Shorter transverse openings in the top of the rubber head allowed some lateral flexion on the rod. A knuckle joint in the neck aided these movements, especially flexion and extension. It was only after these changes had been made in the rubber head that the pelvic curve could be determined. The chain connecting the head to the pelvis was discarded. The rubber shoulders were removed because they were in the way, inasmuch as this head does not really flex on the shoulders at the neck, as is the case in the living fetus. For when the attempt is made to flex the head the rubber shoulders are projected posteriorly because the neck does not bend easily. As the head passes down this curved rod, one can demonstrate its positions and course in normal and abnormal vertex labors and in breech deliveries. Attempts to practice forceps deliveries with this modified rubber head on the pelvic curve rod were not wholly satisfactory. In fact, the best head for forceps work proved to be the leather-covered wooden head of the American-made doll. Recently a spring action has been inserted in the neck of this doll so that it is no longer flaccid. Still more recently



Fig. 1.—Rubber-lined Stander pelvis with bar-holding rod fashioned to pelvic curve.

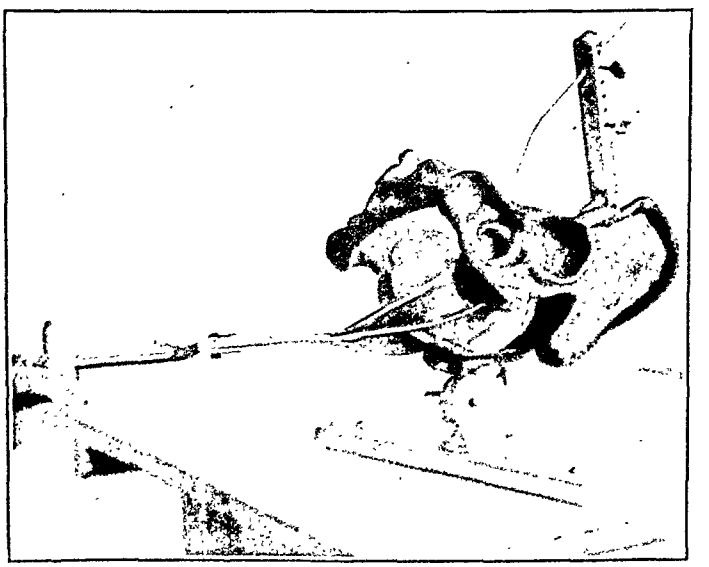


Fig. 2.—Forceps on rubber head in pelvis.

a yielding moldable head with the landmarks preserved has been substituted for the wooden head, to more nearly approximate conditions in the human fetus.

A demonstration possible with this pelvis is the modified Scanzoni maneuver in rotating occipitoposterior positions of the head. Here the forceps blades rotate on their long axis while one observes the sweep taken by the handles. A forceps must be sacrificed for ordinary use by having two bars fastened between the blades in the line of their long axis. Then a straight rod (Fig. 3) is run through holes in the centers of these two bars and the forceps blades are rotated on this rod, while the handles sweep around in an arc which Bill has described and pictured clearly. To make this more realistic the rod is attached to the bar above the pelvic inlet so that the forceps blades rotate on their long axis within the pelvis. This demonstration had been attempted in former years by the use of various instruments with obtuse angles, such as a bandage scissors or a greenstick fracture of an applicator or a match. The shorter part, representing the forceps blades, was made to rotate on its long axis; at the same time the longer end swung round like the handles. The bar above the pelvic inlet may be removed quickly at any time so as to allow of better manipulation with a dead fetus or a doll.

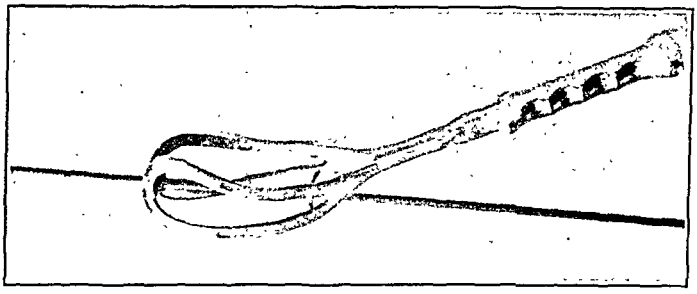


Fig. 3.—Rod through bars in line of long axis of forceps blades.

Since its introduction the Stander obstetric phantom has seemed to be a popular choice. Points in its favor are that it is extremely durable and is not expensive. The modifications of this pelvis here presented make it possible to use with it any forceps without danger of scratching the instrument and allow us to compare different makes of forceps with one another. Other changes permit demonstrations of the modified Scanzoni maneuver and of the descent of the head along the pelvic curve.

Thanks are due to Mr. Joseph P. Faulkner, chief engineer of Mountainside Hospital, to Mr. Wilhelm B. Bronander of the Bronander Engineering and Research Corporation, Arlington, N. J. and to the makers of the pelvis, the Clay-Adams Company, Inc., New York.

21 Plymouth Street

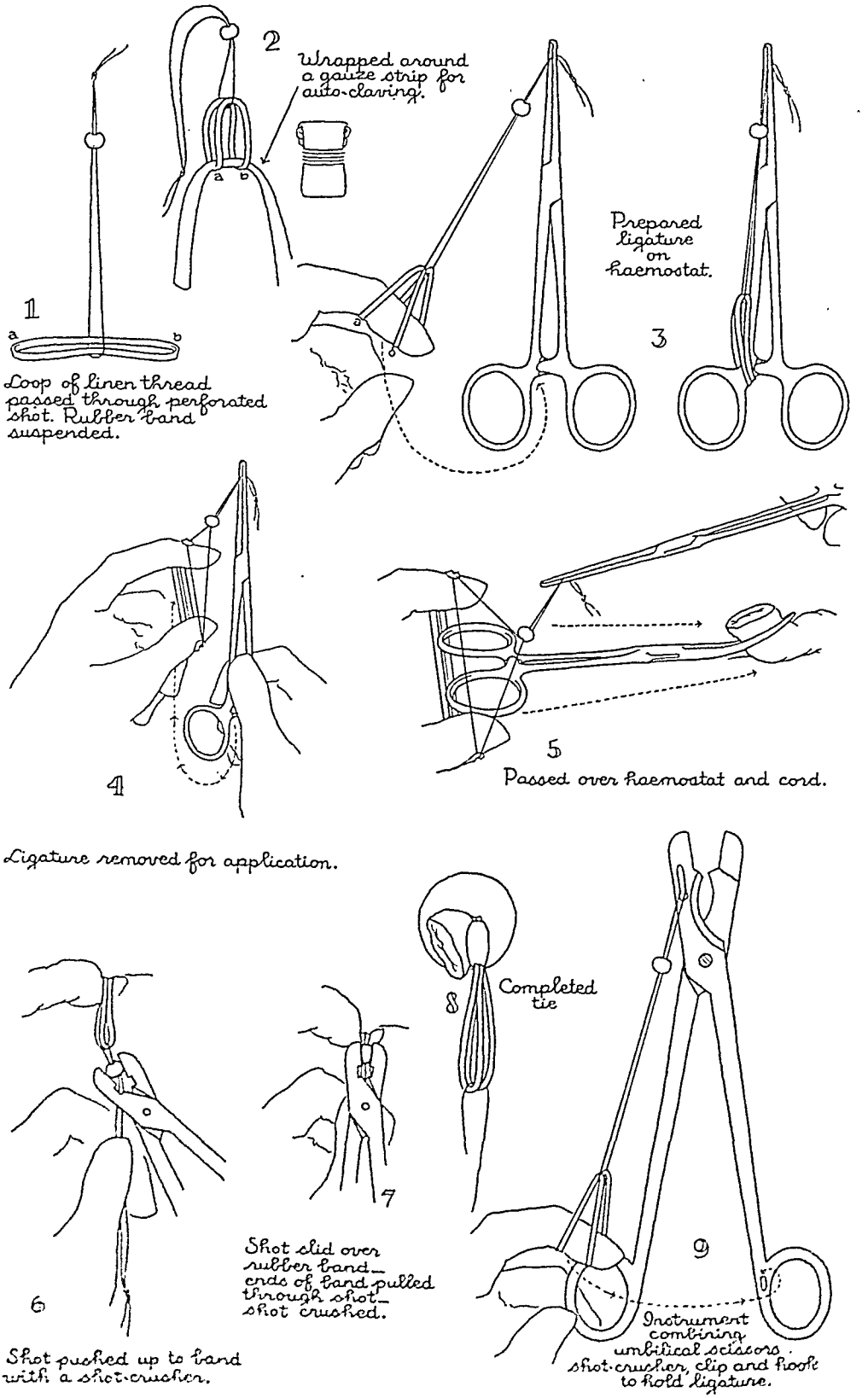
A SIMPLE, SAFE AND ECONOMICAL CORD TIE

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EVERY practicing obstetrician has experienced the need for a comprehensive instrument or appliance to replace ligation of the umbilical cord in the newly born infant, and a careful study of the many varied types already devised revealed none which would adequately satisfy all requirements.

In response to the search for quick simplicity with safety at a minimum expense, a method has been devised by me which has been found to provide all the necessary attributes required of such a tie or clamp. It provides complete asepsis, proper hemostasis with good wound healing, and it permits easy care and dressing. In addition, there is no dangling weight on the cord and it does not cut or tear.


1
a
b
Loop of linen thread passed through perforated shot. Rubber band suspended.
2
a
b
Wrapped around a gauze strip for auto-claving.
3
Prepared ligature on haemostat.
4
Ligature removed for application.
5
Passed over haemostat and cord.
6
Shot pushed up to band with a shot-crusher.
7
Shot slid over rubber band— ends of band pulled through shot— shot crushed.
8
Completed tie
9
Instrument combining umbilical scissors, shot-crusher, clip and hook to hold ligature.

FIGS. 1 to 9.

The tie is made of a loop of linen thread, a perforated lead shot and a rubber band, arranged as in Fig. 1. These are wrapped around a piece of gauze for convenience in autoclaving (Fig. 2).

At the time of delivery, the tie is removed from the gauze and arranged as shown in Fig. 3, a hemostat clamping the free end of the thread loop, the rubber band being placed over the handle of the hemostat.

After the umbilical cord is clamped and cut, the rubber band is removed and stretched out with the fingers (Fig. 4). It is passed over the clamped cord and placed as close as possible to the skin (Fig. 5). The shot now is grasped lightly with the shot-crusher and held in a fixed position close to the cord (Fig. 6); and the rubber band is pulled through the perforated shot with a firm and continuous pull on the linen loop (Fig. 7) until the rubber band constricts the cord sufficiently to produce a definite blanching which occurs when enough tension has been applied. The shot is then crushed to hold the rubber tie in place. Thoroughness here is important. The remainder of the cord is cut about one-half inch above the tie (Fig. 8). The ends of the loop may then be cut off or used to hold a cord dressing.

At no time is there any pull on the cord itself. The rubber band does not tear or cut into the umbilical cord and, because it contracts as the cord shrinks, consistent pressure is maintained.

The evolvement of this method has prompted the construction of an instrument combining umbilical scissors and shot-crusher with a clip and hook to hold the described ligature (Fig. 9).

In 239 cases* this tie has been used with no adverse results. Separation of the cord occurred naturally on an average of six days after application. This incidence was variable at different institutions where it was applied by internes, nurses, or doctors with differing types of rubber bands and shot. This experience has demonstrated that use of No. 32 rubber band and 7½ mm. lead shot, with 4 mm. perforation, insures the most favorable results. It will readily be appreciated that in this type of tie the quickest separation occurs when the greatest tension is applied.

The cases here cited were observed with parallel application of Zeigler clamps in 77 cases, in which separation occurred on an average of four days; and 50 cases in which umbiliclamps were used, separation occurring on an average of seven days in these cases. Healing is almost identical when this tie or the Zeigler clamp is used, and somewhat more favorable than the umbiliclamp, with which exudate and granulation tissue usually appears.

The newer method here detailed has proved so successful that I believe its trial will convince obstetricians of its economy, efficiency, and complete satisfaction.

*1176 additional patients have been treated successfully without complications since the above report.

Special Article

WILLIAM SHIPPEN, JR.

The Great Pioneer in American Obstetrics

Herbert Thoms, M.D., New Haven, Conn.

WILLIAM SHIPPEN, JR., of Philadelphia is the great pioneer in American Obstetrics for he was the first lecturer on that subject in this country and the first to establish a hospital for such instruction. His early course of anatomical lectures, 1762 and 1763, represents in fact the beginnings of medical teaching in America.

Shippen belongs to that comparatively small group of men in medicine who are famous sons of famous fathers. His father of the same name was descended from Edward Shippen, a member of the Society of Friends who emigrated to Boston from Cheshire, England, in 1668. At the request of William Penn this ancestor soon removed to Philadelphia and as first mayor of that city is said to have become distinguished as having three great things: "the biggest house, the biggest person, and the biggest coach." Edward's son Joseph married Abigail Grosse and William Shippen (Sr.) was born to them Oct. 1, 1712. He was wholly educated in his native city and became a leader in medicine in his time. He was the first physician to the Pennsylvania Hospital, a founder of the University of Pennsylvania, and a founder of the College of New Jersey (Princeton University). In 1778 he was elected to the Continental Congress and he was one time vice-president of the American Philosophical Society.

William Shippen, Jr., was one of four sons born to Susannah Harrison and William Shippen, and was born in Philadelphia Oct. 21, 1736. As a boy he attended the Rev. Samuel Finley's academy in Nottingham, Pa. This school was one of the important educational influences in colonial America and its proprietor subsequently became President of the College of New Jersey. Among fellow students of William Shippen at the academy were John Morgan and Benjamin Rush. From Nottingham the young Shippen entered the College of New Jersey, then under the presidency of Aaron Burr, father of the Vice-President of that name. In 1754 he received his bachelor's degree and at commencement was chosen to deliver the valedictory address. The great preacher, George Whitefield, an auditor on that occasion, is said to have been so impressed that he urged the young orator to enter the pulpit. Shippen's mind, however, was set on the profession of his father and he returned to Philadelphia where he studied until 1758 at which time he went abroad to complete his education. According to Watson, quoted by Packard, a letter written by his father at this time to an English correspondent reads, "My son has had his education in the best college in this part of the country, and has been studying physic with me, besides which he has had the opportunity of seeing the practice of every gentleman of note in

our city. But for want of that variety of operations and those frequent dissections which are common in older countries, I must send him to Europe. His scheme is to gain all the knowledge he can in anatomy, physic, and surgery." The young student's "scheme" could hardly have failed in the environment in which he found himself shortly after arriving in England. His first residence in London was in the family of John Hunter who at that time was assisting his brother William in the latter's anatomical theater. By means of this association he became friendly with William Hewson and Sir John Pringle, and also at this time came under the notice of Dr. John Fothergill. Fothergill, born of a Quaker family and a leading London physician, had a great interest in the Pennsylvania Colony and in the newly established Pennsylvania



William Shippen, Jr. (From a portrait in the College of Physicians, Philadelphia.)

Hospital. He was also greatly interested in the young man who was planning to carry the latest teachings of the old world to the new. At the expense of 200 guineas Fothergill employed the artist Rensdyck to execute drawings of anatomical structures. The dissection for this purpose is said to have been made by an anatomist named Jenty and John Hunter is reported to have had a hand in the enterprise. These pastel drawings, eighteen in number, and three plaster of Paris castings of the abdomen of a pregnant woman were presented to the Pennsylvania Hospital and today are among the choice possessions of that institution.

William Shippen had a particular interest in midwifery and attended for a time lectures given by Colin Mackenzie, a one-time pupil of Smellie. Shippen received his medical degree from Edinburgh, the title of his thesis being "De Placentae cum Utero Nexu." While in the northern

capital his opportunities were enriched under the instruction of Munro Primus and Cullen. From the foregoing and what I shall mention in following it seems probable that no young man of colonial America who went abroad to study medicine ever had a richer experience or came into finer contact with the great masters of that day. William Shippen was apparently one of those fortunates who are "born aright in time and place."

After finishing his studies at Edinburgh his desire was to continue studying in France. That country was then at war and this trip was made possible only after his friend Sir John Pringle had secured for him a position as travelling physician to a lady journeying to southern France for her health. He resided for a short time in France and while there apparently met among other notables that genius of literary obstetrics, Laurence Sterne, for in a letter written to David Garrick from Paris in March, 1762, Sterne writes, "This will be put into your hands by Dr. Shippen who has been here some time with Miss Poyntz and is this moment setting off for your metropolis."

While in London Shippen had become engaged to Alice Lee, daughter of the Honorable Col. Thomas Lee, acting governor of the Colony of Virginia. She was the sister of Richard Henry Lee and Francis Lightfoot Lee, both of whom were "Signers." Following the death of her parents she had gone to live with her uncle, Philip Ludwell III, in London. Among the circle of friends whom William Shippen found in this household may be mentioned, Fanny Burney, Dr. Samuel Johnson, Boswell, John Paradise, and his own benefactor John Hunter. His marriage took place April 3, 1762, at the Church of St. Mary Le Strand, Middlesex. Within a few days the bride and groom sailed for America where a new house was awaiting them, a present from William Shippen, Sr. This house, which is still standing at the corner of Locust and Spruce Streets, was to become an important landmark in the history of our country and expresses, says a writer, "the quiet dignity and well being of the life of the early American aristocracy." The Fothergill drawings came to America soon after Shippen's arrival in May, 1762, and the donor in a letter to James Pemberton mentioning Shippen says, "that he is well qualified—that he will soon be followed by an able assistant, Doctor John Morgan, and, that if countenanced by the legislature they will be very useful, and erect a school of medicine." At the time of Shippen's arrival in Philadelphia in practice there besides his father were the brothers Thomas and Phineas Bond, Thomas Cadwalader, John Redman, and Cadwalader Evans.

Shippen's plans for lecturing were not delayed for in a newspaper letter of Nov. 11, 1762, he stated "that a course of anatomical lectures will be opened this winter in Philadelphia for the advantage of the young gentlemen now engaged in the study of physic in this and the neighboring provinces, whose circumstances and connections will not permit of their going abroad for improvement to the anatomical schools in Europe; and also for the entertainment of any gentlemen who may have the curiosity to understand the anatomy of the human frame. In these lectures the situation, figure, and structure of all the parts of the human body will be demonstrated, their respective uses explained, and as far as a course of anatomy will permit, their diseases, with the indications and methods of cure briefly treated of. All the necessary operations in surgery will be performed, a course in bandaging exhibited, and the whole concluded with the explanation of some of the curious

phenomena that arise from an examination of the gravid uterus, and a few plain general directions in the study and practice of midwifery. The necessity and public utility of such a course in this growing country, and the method to be pursued therein, will be more particularly explained in an introductory lecture, to be delivered on the sixteenth instant, at six o'clock in the evening, at the State House, by William Shippen, M.D."

The first course of lectures was attended by twelve pupils. The opposition of the public to dissection was demonstrated on several occasions by the smashing of windows in the house where they were performed. The young lecturer sought to soothe this antagonism by announcing in the press that the bodies so used were those of criminals who had been legally executed and "now and then one from the Potter's Field."

Three years later, in 1765, William Shippen began the first systematic lectures on obstetrics which were given in this country. These were illustrated by the "anatomical plates and casts of the gravid uterus at the hospital." The *Pennsylvania Gazette* of Jan. 1, 1765, carried the following advertisement: "Dr. Shippen, Jr., having been lately called to the assistance of a number of women in the country in difficult labors, most of which were made so by the unskilful old women about them; the poor women having suffered extremely, and their innocent little ones being entirely destroyed, whose lives might have been easily saved by proper management: and being informed of several desperate cases in the different neighborhoods which had proved fatal to the mothers as well as to their infants, and were attended with the most painful circumstances, too dismal to be related! He thought it his duty immediately to begin his intended courses in Midwifery, and has prepared a proper apparatus for that purpose, in order to instruct those women who have virtue enough to own their ignorance and apply for instruction, as well as those young gentlemen now engaged in the study of that useful and necessary branch of surgery, who are taking pains to qualify themselves in practice in different parts of the country with safety and advantage to their fellow citizens." Some idea of the conditions prevailing in the obstetrics of that day may be gained from a statement by Shryock who observes, "Maternity cases were left, in English speaking lands, almost entirely to midwives. Despite the general coarseness of the age, the attendance of men upon maternity cases was held to be most indelicate. The apparent paradox may possibly be explained in terms of matrimonial jealousy and suspicion. Whatever the explanation, the fact remains. And since midwives lacked any scientific training, obstetrics proceeded on the level of folk practice with consequences which may easily be imagined."

Shippen established what was practically a lying-in hospital in providing "convenient lodgings" for a few poor women, "under the care of a sober, honest matron, well acquainted with lying-in women." He also informs his prospective pupils that he will "be able to present each of you with one natural labor at least, and have provided a machine, by which I can demonstrate all kinds of laborious and preternatural labor, and so give every necessary direction to enable you to manage all cases with the greatest safety to mother and child."

On May 3, 1765, the Trustees of the College of Philadelphia having considered John Morgan's project to establish a medical school gave the plan approval and elected him Professor of the Theory and Practice

of Medicine. This was the beginning of the medical department of the University of Pennsylvania. In September of the same year William Shippen was elected Professor of Anatomy and Surgery. Anatomical lectures were given by him regularly until the fourteenth course which was in the winter of 1775 when the War of the Revolution caused their suspension. Wistar says regarding Shippen's manner of teaching, "He went through the substance of each preceding lecture by interrogation, instead of recapitulation, thus fixing the attention of the students—and his manner was so happy, that this grave process proceeded like a piece of amusement." The public interest in Shippen's lectures and demonstrations is shown by a notation in John Adams' diary which reads, "Dr. Shippen carried us into his chamber where he showed a series of anatomical paintings of exquisite art. Here was a great variety of views of the human body; whole and in part. The Doctor entertained us with a clear, concise, comprehensive lecture upon all parts of the human frame. The entertainment charmed me."

In 1779 the legislature repealed the charter of the College of Philadelphia at the time of the creation of the University of Pennsylvania and Shippen became a professor in the new school. In 1783 the charter of the College being restored, for a time he occupied chairs in both schools, and when a consolidation took place in 1791 under the title of the former institution he occupied the chair of anatomy, surgery and midwifery with Caspar Wistar as adjunct professor.

William Shippen's first military position, according to Packard, was that of medical director of the Flying Camp in the Jerseys and as such was under the authority of John Morgan as director-general. A short time after, when Morgan was dismissed as director-general, Shippen was advanced to director of hospitals on the west side of the Hudson River, those on the east side remaining under the authority of Morgan. Subsequently Shippen with the aid of John Cochran, who had seen service as surgeon's mate in the French and Indian wars, outlined a plan of reorganization which was adopted by Congress early in the spring of 1777. On April 11 of that year according to Brown, quoted by Graves, "To the position of Director General, Dr. Philip Turner of Connecticut was at first nominated and elected, but before adjournment a reconsideration was moved, and it was urged with great propriety that the author of the plan had claims, not only of great distinction in his profession, but of previous service, which were superior to those of others. Accordingly a new election being held, Dr. William Shippen received the unanimous vote of all the thirteen states." It is not within the present scope to tell of Shippen's military career. We can but mention his famous court-martial, instigated largely by Rush and Morgan, which resulted in his aquittal on all counts and following which the commander-in-chief publicly thanked him for his excellent service. To those interested in this dramatic and historic episode reference is directed to Gibson's excellent volume on the medical background of the Revolution. Shippen attributed the animosity of both Rush and Morgan to the belief that he had forced them out of military preferment. It is interesting to note with regard to the former that time probably healed these ugly wounds for in Rush's diary of July 11, 1806, it is recorded, "Shippen died today! I attended him in his last illness." Shippen remained as Director General until January, 1781, at which time he resigned and resumed his teaching and practice. In obstetrics he succeeded in combating the prejudice against men in this branch to such an extent that he secured a large clientele.

In 1798 a great tragedy of his life occurred in the death of his only son. Wistar says this "cut the sinews of his exertions, and left him gradually to wither—the amiable victim of paternal affection." He lectured but occasionally after this and his practice declined. However, toward the latter part of his life his interest in medicine seemed to return, and we find an account of him again giving his introductory lecture in new buildings now to a class of nearly four hundred. In 1808, his debility returned and he removed to Germantown where he passed away the eleventh day of July.

The men with whom we associate the word great are usually those whose contributions are of a twofold nature, namely, the things that they did and the lives that they influenced. William Shippen established the teaching of clinical obstetrics in this country and his influence on hundreds of his pupils extended throughout the then settled America. When we consider the conditions which faced him in the doing of this task, we must believe that, as it was said of William Smellie: "Man midwifery was the idol of his heart." In considering Shippen's early establishment of a teaching hospital it is interesting to note that it was not until after his return from abroad that the first institution especially esablished for instruction in obstetrics was founded in London (1765).

William Shippen, eminent in the establishment of anatomical teaching and the development of military medicine, remains the Great Pioneer in American Obstetrics.

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After exhaustive studies the authors came to the conclusion that the amniotic fluid constitutes a very good medium for the growth of micro-organisms. Because of its encapsulation, 91 per cent of 22 specimens of amniotic fluid were found to be sterile. The *Bacillus perfringens* was discovered in 2 of the 22 patients, although they had intact membranes.

MARIO A. CASTALLO.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

BIRTH AND MORTALITY STATISTICS

IN A RECENT review of the birth and mortality statistics for the United States, Tandy[1] has pointed out many interesting facts. Especially significant are the comparisons between the statistics for 1915 and 1936. The birth rate (16.7 per 1000 estimated population) in 1936 was lower than in any other year except 1933 (16.5) and consequently over 1,000,000 fewer infants were born than would have been expected had the 1915 rate (25.1) prevailed. The stillbirth rate in 1936 was 34 per 1000 live births which is slightly lower than the rate (36) for the preceding two years. Figures for 1915 are not available for comparison. The infant mortality rate was 57 per 1000 live births, lower than that for any preceding year except 1935 (56). The rate (100) in 1915 was almost twice as high. Had this rate prevailed in 1936, 92,000 more infants would have died during that year. The provisional rate for 1937 is 54 per 1000 live births and indicates that the final 1937 infant death rate will probably be the lowest on record. The neonatal mortality for 1915 was 44 per 1000 live births, while in 1936 it had decreased to 33. Mortality on the first day of life has not decreased and was 15 in both 1915 and 1936. The maternal mortality rate of 57 per 10,000 live births is the lowest ever recorded in the United States. This was the seventh consecutive year in which the maternal mortality rate decreased slightly. Among the 24 countries for which information is available only four have higher rates than the United States. The European countries with the lowest rates are Norway (28 per 10,000 live births, 1935), Netherlands and Italy (30, 1936 provisional rate), Irish Free State (32 in 1937), Sweden (33 in 1934). The differences in procedures for assigning cause of death are not sufficient to account for the rate in the United States which is high as compared with most foreign countries.

The largest number of births, stillbirths and maternal deaths occurred among mothers 20 to 29 years of age, the next largest was among those 30 to 39 and the smallest number among those 40 years or over. The maternal mortality and stillbirth rates by age of the mother, however, are much higher among extremely young mothers and those 40 years or over. The stillbirth rate (67 per 1000 live births) was highest among mothers under 15 years of age and lowest (30) among those from 20 to 29. The highest maternal mortality rate was for mothers 40 years or over (146 per 10,000 live births) the lowest (38) was for mothers 20 to 24 years of age.

Of the infant deaths in 1936, 53 per cent occurred during the first month of life, 47 per cent from the first to the twelfth. Death in the first month was due mainly to natal and prenatal conditions (81.1 per cent). Premature birth (14.64 per cent) was the most common condition designated as the cause of death, while injury at birth (13.6 per cent), congenital malformations (10.4 per cent), and other causes (10.6 per cent) made up the remainder of the natal and prenatal conditions. Respiratory diseases (5.0 per cent), gastrointestinal (2.4 per cent), other specified causes (5.3 per cent), and unknown or ill-defined causes (6.1 per cent) accounted for the 18.9 per cent of deaths due to other causes than natal or prenatal conditions. Among infants who completed their first month of life but died before reaching one year of age, natal and prenatal conditions were much less important (14 per cent). In 1936 respiratory conditions caused 35 per cent of these deaths, gastrointestinal dis-

[1] *Tandy, Elizabeth C.:* The Child 3: 85, 1938.

eases 23 per cent, epidemic and communicable diseases 7 per cent, all other specified causes 16 per cent, and unknown or ill-defined 5 per cent. Maternal deaths were caused by puerperal infection (38 per cent), toxemia (23 per cent), accidents of childbirth (13 per cent), puerperal hemorrhage (11 per cent), nonseptic abortions (6 per cent), and other causes (9 per cent).

The growing interest in the problem of stillbirths, neonatal and maternal deaths is leading to many special studies regarding these conditions. More widespread application of the remedial measures already recognized to be of value is producing some decrease in all of these conditions. However, since several large communities have been able to decrease the incidence of maternal and infant deaths and stillbirths far below that of the country as a whole, it indicates that by putting into practice what is already known about the prevention of such fatalities greater reductions in the total number of deaths can be made. Sixty-one per cent of the maternal deaths were due to puerperal infection or toxemia. By the use of aseptic technique and by proper treatment during pregnancy and delivery most of these deaths could be prevented. It is believed that one-half the maternal deaths, one-half of the infant deaths and two-fifths of the stillbirths are preventable. Giving all mothers the full benefit of our present knowledge would save almost 1,000,000 lives each year.

Simon, C.: Chancres of the Uterine Cervix Accompanied by Palpable Pelvic Adenopathy, Presse méd. 55: 1085, 1938.

Recently, in each of three patients with proved chancre of the cervix, the author palpated a firm, spherical, cherry-sized elusive mass in the lateral pelvic wall, and he interpreted this as representing regional adenopathy of the primary lesion. To detect the gland the slightly flexed examining fingers should be placed deeply in the lateral fornix against the osseous surface of the true pelvis and be drawn forward. By means of ingeniously planned x-ray studies it was ascertained that the gland lay approximately 5 cm. from the ischial spine and 2 cm. from the ileopectineal line in a vertical axis passing through the spine. Cadaver dissection verified the clinical and radiologic finding by revealing the presence of a normal lymph node approximately the size of a grain of corn. This node corresponds to the one that Leveuf and Godart described as the "principal ganglion" of the uterine lymphatics. Usually there is a single node, although occasionally there are two.

A thorough review of the world's literature did not reveal any detailed reference to this finding. Fournier, in a description of regional adenopathy in relation to chancre, simply refers to the existence of a "pelvic node" accompanying chancre of the cervix, but parenthetically qualifies it as "theoretical." He adds that except for an occasional bubo there is in general no inguinal lesion. Jeanselme and Lefevre, in their treatise on syphilis, quote the general consensus of opinion that the adenopathy accompanying chancre of the uterine cervix is pelvic, and consequently impossible to detect.

These enlarged pelvic nodes have never been sought because they were always believed to be clinically inaccessible. Simon observed 21 cases of cervical chancre in the past two years, but the thought of searching for the accompanying lymphatic lesion did not occur to him.

This interesting clinical observation confirms the classical belief of Ricord and Fournier in the constancy of the existence of a satellite bubo.

Such an adenopathy may be considered residual evidence of a pre-existing cervical chancre. Knowledge of the fact that the draining lymphatics of the corpus uteri share the efferent vessels of the cervix suggests the possibility of making a diagnosis of intrauterine chancre in the presence of enlargement of this important lymph node.

ARNOLD GOLDBERGER

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF MAY 10, 1938

The following papers were presented:

Ante-partum Rupture of the Uterine Scar Following Low Flap Cesarean Section. Dr. J. Randolph Gepfert (by invitation). (For original article, see page 466.)

A Fifteen-Year Study of Cesarean Section at the Woman's Hospital of New York. Dr. Ralph L. Barrett. (For original article, see page 434.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MAY 20, 1938

The following papers and discussions were presented:

The Manchester (Parametrial Fixation) Operation for Cure of Prolapse and Cystocele. Dr. M. L. Leventhal and Dr. L. D. Boshes. (For original article, see page 384.)

Pregnancy With Leucemia. Dr. R. M. Grier and Dr. H. A. Richter (by invitation). (For original article, see page 412.)

with carbon dioxide; *that of the barbiturates cannot:* a very important point in relation to resuscitation.[5]

The chief inference to be drawn is that only such narcotics as are of relatively brief action are justifiable in labor, and then only in the early stages. In the later stages anesthetics alone should be used; for anesthetics are drugs of brief action and have relatively slight depressive effects upon respiration. Even with anesthetics precautions must be taken against asphyxia. Particularly in the use of nitrous oxide, the percentage of oxygen with which the gas is mixed should not be allowed to fall below 15 per cent.[8] Otherwise asphyxial effects, immediate or delayed, effects essentially like those of carbon monoxide asphyxia, may result.[9]

Even with these limitations much may be done to diminish suffering. But the science of pharmacology affords no means of rendering childbirth free from even the slightest discomfort or recollection in the mothers except at the cost of many dead or damaged babies.

Yandell Henderson.

Sulfanilamide in Obstetrics and Gynecology

CHEMOTHERAPY in the treatment of infections has received a tremendous impetus during the past three years. At no time in medical history has such a promising drug as sulfanilamide and its related compounds been placed in the hands of the medical profession for this purpose. Experience, however, has amply demonstrated a wide variety of toxic symptoms that may occur following its use, some of which are no contraindication to the continuance of the therapy while others less often offer a definite indication to stop the administration of the drug. Exhaustive research in bacteriologic, immunologic, chemical, pharmacologic and therapeutic fields is necessary before we understand some of the most fundamental actions of the drug.

Sulfanilamide is absorbed as rapidly or even more rapidly when taken by mouth than when administered subcutaneously and absorption is more rapid when given on an empty stomach. It is rapidly distributed throughout all maternal and fetal tissues including the placenta, liquor amnii, colostrum and milk. The drug is eliminated from the body almost entirely by the kidneys. No definite deleterious effects on the fetus have as yet been described. In general, treatment is more successful if the patient is hospitalized as the drug is tolerated better with the patient confined to bed and dosage can be more accurately controlled. Toxic signs and symptoms are also recognized earlier than in ambulatory patients. It is usually advisable to give sodium bicarbonate by mouth at the same time to prevent the possible development of an acidosis. There is usually no contraindication to other *necessary* medication at the same time, but its therapeutic action should not mask possible toxic symptoms. Because of the rapid absorption and prompt excretion, a

[8] *Eastman, N. J.:* Ibid. 31: 563, 1936.
[9] *Courville, C. B.:* Medicine 15: 129, 1936.

satisfactory blood concentration can only be maintained by fractionating the daily dose and administering the drug every four hours.

Medical history has again repeated itself in that with the discovery of a new therapeutic agent the clinical application has far exceeded the indications of proved value. Our present understanding which may be radically modified in the future suggests the following indications, manner of use and control in our field.

a. In puerperal and postabortal infection accurate bacteriologic examination of the lochia is an essential prerequisite to treatment. This may be done by examining the lochia obtained from within the uterus or if this is impossible a sample may be obtained by a simple vaginal swab. If a hemolytic streptococcus is present in the material examined a diagnosis can usually be made in from twelve to eighteen hours. This is necessary because only from 1 to 2 per cent of patients classified as morbid in a well-conducted obstetric service are found to have a beta hemolytic streptococcus in the lochia while an additional 2 to 3 per cent may harbor an alpha prime strain. Even in institutions where only the more seriously ill patients suffering from puerperal infection are admitted usually not more than one-third are found to have hemolytic streptococcus infections. Experience to date indicates that sulfanilamide is of definite value only in the treatment of puerperal infection due to a hemolytic streptococcus and has but little if any effect on puerperal infections due to the other usual organisms associated with such infections. Adequate dosage (6 to 8 gm. per day) in divided doses *early* in the disease is essential if the infection is serious.

b. Pyelitis before, during, or after labor. Again accurate bacteriologic examination of the urine is necessary prior to treatment. If total fluid intake is restricted to 2,000 c.c. per day, a satisfactory concentration of the drug may usually be attained by the administration of 3 to 5 gm. daily in divided doses. Good results are frequently obtained in infections due to the colon-aerogenes group of organisms so often associated with such infections. *Staphylococcus albus* and *aureus* organisms may also often be quickly eliminated from the urine. Urinary tract infections due to nonhemolytic streptococci and some of the other gram-positive organisms are usually treated more successfully by mandelic acid therapy. Smaller doses than mentioned above may be used successfully to sterilize the urine following the subsidence of the acute infection.

c. Gonorrhea. No chemotherapeutic agent used before the introduction of sulfanilamide has yielded anything like as satisfactory results in the treatment of this infection. Clinical experience to date has indicated certain facts that must be taken into consideration in order to obtain the best results. The treatment should not be started as a rule before the elapse of at least eight to ten days after the initial onset of the disease. A chronic gonorrhea is often more easily cured than the acute disease. Bacteriologic studies by cultural methods offer the only sound method of controlling the treatment and determining when a cure is established. It is quite possible that the discharge may cease and clinical symptoms disappear soon after starting treatment *but the gonococcus may still be present* in the local secretions. Thus, a state of

chronic carrier could in this way be established, which may be a possible, serious menace to society. The drug must be administered in adequate dosage from the start of the therapy and until repeated cultures become negative. There is definite evidence to suggest both from clinical findings and from laboratory data that the gonococcus may gradually be induced to grow in the presence of increasing concentrations of the drug, the phenomenon of becoming "sulfanilamide fast." It is readily understandable how this can take place in the patient if low dosage is employed. The ideal dosage has not as yet been determined; however, present information suggests that the initial daily dose should approximate 5 gm. The drug should be continued possibly with decreased dosage until three negative cultures at two-day intervals have been obtained. Determination of "cure" purely by clinical methods and smear interpretation is of very dubious value. "Permanent cure" criteria must depend largely on repeated negative cultures at monthly intervals following sulfanilamide therapy.

To sum up, it may be claimed that this new drug constitutes a valuable and noteworthy addition to the materia medica, but further research is necessary to determine its action and limitations as well as proper dosage. Certain unfortunate results which have accompanied its employment, largely in unskilled hands, should call for that caution which is so essential for safe and successful results.

—*R. G. Douglas.*

Announcement

American Association of Obstetricians, Gynecologists and Abdominal Surgeons Annual Foundation Prize

The American Association of Obstetricians, Gynecologists and Abdominal Surgeons announces that the annual Foundation Prize for this year will be $100.00. Those eligible include only (1) interns, residents, or graduate students in Obstetrics, Gynecology and Abdominal Surgery, and (2) physicians (M.D. degree) who are actually practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

Competing manuscripts must (1) be presented in *triplicate* under a nom de plume to the Secretary of the Association before June 1, (2) be limited to 5,000 words and such illustrations as are necessary for a clear exposition of the thesis, and (3) be typewritten (double-spaced) on one side of the sheets, with ample margins.

The successful thesis must be presented at the next annual (September) meeting of the Association, without expense to the Association and in conformity with its regulations.

For further details, address Dr. James R. Bloss, Secretary, 418 11th Street, Huntington, W. Va.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Gynecology and Obstetrics

The tenth volume of *Stoeckel's Handbuch der Gynaekologie*[1] has appeared in three fasciculi of, respectively, 738, 438, and 1008 pages. This tremendous production appears to be from the pen of Stoeckel alone.

The first fasciculus covers the anatomy and function of the urinary tract. He considers ureteral antiperistalsis an artificial product and states that damage to the urethral control of the detrusor and sphincter are always inseparable. The changes occurring during pregnancy, labor and puerperium are taken up. In describing diagnostic methods, very little emphasis is placed on intravenous pyelography. A very full description of congenital anomalies follows. Stoeckel is unconvinced that Hunner's ureteral strictures or elusive ulcers occur, but is willing to search for focal infections. The chapter on cystitis is full, as is the very detailed one dealing with endometriosis of the bladder. Although all the well-known methods of treatment of pyelitis are described, the author does not give any decided personal preference. The rarer conditions of gonorrhea, syphilis and lymphogranuloma of the urethra and bladder conclude this portion.

Fascicle II describes tuberculosis of the genitourinary organs, which is always of the descending type. Ten per cent of all tuberculosis deaths are due to urinary infection. However, in contradistinction to the male, no cross infection from the urinary to the genital tract or vice versa takes place in the female. According to Stoeckel, spontaneous healing of kidney tuberculosis does not occur. Pregnancy is no contraindication to operation for tuberculosis of the urinary tract.

Injuries and fistulas of the urinary tract are next taken up. For incontinence, various sphincter plastics are discussed with particular emphasis on the Stoeckel-Goebell technique. The causation and situation of fistulae, the techniques for their repair including the abdominal route and reconstruction of destroyed urethra are described in great detail.

Fascicle III covers ureter fistula and a very minute discussion of the precautions advocated to avoid ureter injuries during vaginal as well as abdominal operation. In special instances, placing the kidney out of function by means of x-ray has been advocated for the relief of ureteral fistula. The author takes no decided stand as to the advisability of this measure. In transplantation of the ureter, Stoeckel prefers the intraperitoneal route with transplantation into the sigmoid. The discussion likewise covers foreign bodies in the kidney, ureter, and bladder. Other subjects are prolapse of the urethra and bladder, tumors of the genitourinary tract, including those of the ureter and bladder. Radical cystectomy is thoroughly discussed and beautifully illustrated, likewise treatment of malignancy with radium and x-ray. The causes of hematuria as well as tumors of the ureters, pelvis, and kidney, are described; the discussion of kidney tumors is limited to the author's personal experience. The reader being referred to books on urology for more extensive descriptions. A very closely printed condensed bibliography covering 320 pages closes the last fascicle.

[1] **Stoeckel's Handbuch der Gynaekologie.** Dritte, voellig neubearbeitete und erweiterte Auflage. Zehnter Band. Gynaekologischer Beitrag zur Urologie von Dr. W. Stoeckel, Universitaet Berlin, vol. I, 738 pages with 432 illustrations; vol. II, 438 pages with 261 illustrations; vol. III, 1,008 pages with 468 illustrations. Verlag von J. F. Bergmann, Muenchen, 1938.

This tenth volume is a tremendous contribution, particularly when considered that it comes from the pen of a single author. There are more than 1100 illustrations of which a large number are in color. Of particular beauty are the colored cystoscopic drawings. It is to be regretted that the author has seen fit to keep himself so sedulously in the background, as with his own huge personal experience, most readers would probably have preferred a more subjective presentation. However, these monographs must be considered an extremely valuable contribution to gynecologic and urologic literature.

—*R. T. Frank*

The *Essentials of Obstetrical and Gynecological Pathology*[2] by Marion Douglass and Robert L. Faulkner is a brief monograph in which sufficient text is given to explain the numerous illustrations. Its object is to explain by formal training the pathology of gynecology and obstetrics to the house staff and students. The monograph covers the subjects most adequately in briefest compass. The illustrations are excellent and well selected. This booklet is to be highly recommended for the purpose aimed at.

—*R. T. Frank*

The third edition of Curtis' *Textbook of Gynecology*[3] has appeared. This is the third edition in eight years. In this edition anatomy and physiology have been introduced. Most beautiful and accurate anatomic drawings accompany this portion of the text. The endocrine glands have been taken up in detail as far as these apply to the gynecologic sphere, and although these chapters are purposely short, good judgment has been shown in summarizing the latest knowledge and presenting it in understandable form.

This book is distinguished by its conciseness without sacrifice of completeness and readability. The bibliographic references have been chosen with a great deal of judgment. Curtis' textbook will prove of use not only to the student and practitioner but to the specialist who will find much of interest within its pages.

—*R. T. Frank*

The Book Review Department of the AMERICAN JOURNAL OF OBSTETRICS & GYNECOLOGY takes pride in promptly reviewing such books as are received. According to a letter received recently with *Gynecological Operations*[4] by Fox and Ibarra, a copy was sent for review in 1936 but did not reach our office. This will explain the review of a book published two years ago.

This textbook on gynecologic operations is complete, showing various incisions, both abdominal and vaginal. In perineorrhaphy the levators are exposed and sutured by one technique although other techniques such as the Tait flap splitting are likewise described. Vulvectomy, both the simple and the more radical operation, with removal of the inguinal glands en masse, is given. Bladder fistulas, ureteral transplantation, the formation of an artificial vagina by means of Pallazo's technique (utilization of the labia) as well as Baldwin's operation are described.

In supravaginal hysterectomy both what they call the American method, in which the bladder is first liberated before tying the uterine arteries, and the French technique, in which this step is not performed, are described. Varicocele of the broad ligament is depicted. A thorough description of the Wertheim operation for carcinoma, with every step indicated, will be found.

This book has a running text, is extremely detailed, well executed with ample illustrations for every operative step. The format is faultless.

—*R. T. Frank*

[2]**Essentials of Obstetrical and Gynecological Pathology, with Clinical Correlations.** By Marion Douglass, M.D., Assistant Professor of Gynecology, Western Reserve University, and Robert L. Faulkner, Senior Clinical Instructor in Gynecology, Western Reserve University. With 148 illustrations, 187 pages. The C. V. Mosby Company, St. Louis, 1938.

[3]**Textbook of Gynecology.** By Arthur Hale Curtis, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School, etc. Third edition, reset; 603 pages with 318 illustrations. W. B. Saunders Company, Philadelphia, 1938.

[4]**Ginecologia Operatoria.** Indicaciones y tecnica. Par Eduardo A. Fox y Jose A. Ibarra, Servicio del Hospital Rivadavia, Buenos Aires. Ancleto Lopez, editor, Buenos Aires, 1936.

DeLee's *Principles and Practice of Obstetrics*[5] has appeared in its seventh edition, in itself not a surprising fact but actually a most noteworthy achievement. This volume now has reached the respectable age of twenty-five years and during this quarter of a century has consistently remained in the front ranks among all textbooks on obstetrics. Each succeeding edition has not only proved the thorough familiarity of its author with all progress in this special field of medicine but as well has demonstrated how much of this progress is due to DeLee's own investigations and observations.

Addition of new material, elimination of obsolete matter, changes in the illustrations and the rewriting of various chapters necessitated resetting of the entire book in this seventh edition.

—Hugo Ehrenfest

Diseases of Women[6] by Ten Teachers, edited by Clifford White, is a sixth edition. Three new authors have taken the place of others, Messrs. Goodwin, Gilliatt, and Wrigley.

The text is short, simple and very well illustrated. Completely rewritten are the chapters on the physiology and disorders of menstruation. A short chapter on contraception and sterility has been put into this new edition. On the whole the methods advocated are current in this country. In perineorrhaphy, suture of the levator muscles is still advocated although this gives a painful, nonresilient perineum in many instances.

—R. T. Frank

The Health Organization of the League of Nations has gotten out a small handy *Atlas*[7] illustrating the division of cancer of the uterine cervix into four stages, according to the anatomic clinical extent of the growth. The short introductory texts are in English, French, and German. The charts are simple outlines of the pelvis in its three dimensions and for each stage the various possible sites of carcinoma are plainly indicated in red. This Atlas should be of great help in making international statistics classifiable and concordant.

—R. T. Frank

A short monograph on the cycle occurring in the vaginal mucosa of the human being by G. di Paola[8] is based on biopsies obtained from 71 patients, which include children, mature and pregnant women, and after the climacteric. Vaginal smears were likewise made. The author found no regular cycle. He agrees with Lindeman and Stieve that the differences noted are ascribable to desquamation and repair. In pregnancy the changes are not sufficiently pathognomonic to warrant a diagnosis. In the menopause the regressive changes are progressive. Injection of estrogens produced marked changes in the climacteric vagina. The vaginal threshold to estrogen is much lower than the endometrial threshold.

—R. T. Frank

Casas' short monograph on *Leucoplakia of the Vulva*[9] is based on twenty cases seen in ten years. The ages of the patients were between forty and sixty-five years. He prefers surgery followed by estrogenic therapy to any other treatment. This is a short, well illustrated and complete monograph containing nothing new.

—R. T. Frank

[5]**The Principles and Practice of Obstetrics.** By Joseph B. DeLee, Professor of Obstetrics and Gynecology, emeritus, University of Chicago, etc. With 1,277 illustrations on 985 figures, 271 of them in color, 1,211 pages. Seventh edition, entirely reset. W. B. Saunders Co., Philadelphia, 1938.

[6]**Diseases of Women.** By Ten Teachers, under the direction of Clifford White. Edited by Sir Comyns Berkeley, Clifford White and Frank Cook. Illustrated, 492 pages. Sixth edition. William Wood & Company, Baltimore, 1938.

[7]**Atlas** (English). Illustrating the division of cancer of the uterine cervix into four stages. (Francais) Sur la division des épithéliomas du col de l'utérus en quatre stades. (Deutsch) Über die Einteilung der Kollum-Karzinome des Uterus in vier Stadien. J. Heyman, M.D. Radiumhemmet, Stockholm. League of National Health Organisation. Inquiry into the Results of Radiotherapy in Cancer of the Uterus. Stockholm, 1938. P. A. Norstedt and Söhner.

[8]**El Ciclo de la Mucosa Vaginal en la Mujer.** Par Guillermo di Paola. Illustrated, 76 pages. Editor: El Ateneo, Buenos Aires, 1938.

[9]**Leucoplasia de la Vulva.** Par Pedro Figuerosa Casas, professor adjunto de Clinica Ginecológica de la Facultad de Ciencias Médicas de Rosario, etc. Liberia y editorial Ruiz, Rosario, 1937.

Evolving from a series of staff lectures in his hospital, Dr. Falk publishes his lecture material in *Practical Clinical Gynecology.*[10] This material has previously appeared in serial form in the *American Journal of Surgery.* In successive chapters he defines, discusses, and illustrates the methods of examination and the technique employed in treating pelvic pathology in his service at the Harlem Hospital. Two chapters are devoted to the examination of the patient and operative routine, after which the various major subdivisions of gynecologic diseases are taken up in brief fashion as to pathology, symptomatology, and treatment. Particularly Dr. Falk has defined the indications for operation on his service for these various pathologic conditions. Many of the operative procedures are illustrated. The final chapter describes the technique and methods of the ambulatory or clinic service and discusses minor infections and local procedures.

—*Philip F. Williams*

Samuel's *Endogen Endocrine Therapy in Gynecology and Etiological Treatment of Carcinoma*[11] does not lend itself to serious review.

Quotations from the accompanying announcement to his colleagues will show why I say this. "After my experiments had proved that cancer is caused by the hypophysis I succeeded with the aid of the endocrine electrodiagram in demonstrating that carcinoma is invariably a consequence of primary or secondary thyreotropic hyperpituitarism.

"I came to the conclusion that instead of 15 or more hormones being formed in the hypophysis there are only two: the one which accelerates cell breathing, also known as the thyreotropic hormone, and the one which retards cell breathing, the gonadotropic hormone."

The diagnoses are made by means of a modified spectroscope which shows oxyhemoglobin reduction and meth-hemoglobin. The main basis of his theme is that carcinoma is caused through dysfunction of the hypophysis. He claims to cure even liver metastasis with short wave to the hypophysis. In my opinion this appears to be a worthy successor to Abraham's method.

—*R. T. Frank*

Der Zyklus der Frau[12] by Dr. Jules Samuels, written for lay consumption, offers a new method of determining the time of ovulation, presence of pregnancy, and the problems of menstruation with both normal and abnormal women.

The proposed simple examination by which these conditions may be determined is made possible by the use of a new instrument, the "cycloscope." This consists of a spectroscope and a powerful lamp mounted on a stand with an examining platform upon which the patient's hand is to be placed. This test is made by examining the delicate tissue between the thumb and forefinger with relation to the spectroscopic changes in the oxyhemoglobin content of the blood as it passes this point. The reduction time figured by changes in the spectroscopic analysis of the blood viewed through the instrument is believed to bear a very definite relation to the hormone content of the blood of the woman.

—*Philip F. Williams*

This monograph, *Grundlagen der gynaekologischen Kurzwellentherapie*[13] has appeared as a supplemental number to the *Zeitschrift für Geburtshilfe und Gynäkologie,* Vol. 117. Dr. Raab explains the fundamental physical principles of the short wave, its differences from other modes of heat production and the explanation of the biologic effects produced in the body through its use. He discusses the possibility

[10]**Practical Clinical Gynecology.** By Henry C. Falk, M.D. Clinical Professor of Gynecology, New York University College of Medicine, etc. Illustrated, 293 pages. American Journal of Surgery, New York, 1938.

[11]**Endogene Endokrinotherapie in der Gynaekologie. Aetiologie und Behandlung des** Karzinoms. Von Dr. Jules Samuels, Chirurg und Frauenarzt in Amsterdam, etc. 182 pages. A. W. Sijthoff's Uitgeversmaatschappij, N. V. Leiden, Holland, 1938.

[12]**Der Zyklus der Frau.** Reform Des Ehelebens. von Dr. Jules Samuels, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie. Haag—G. Naeff, Amsterdam, 1938.

[13]**Grundlagen der gynaekologischen Kurzwellentherapie.** Von Dr. med. Ernst Raab, Berlin. With 29 illustrations, 66 pages. Ferdinand Enke Verlag, Stuttgart, 1938.

of harmful influences and methods of application, calculation and indication of certain dosages and the types and technique of the various methods of application through body plates and other forms of electrodes.

Taking up the treatments of gynecologic disorders he discusses the use of this type of therapy, in inflammatory conditions, and mentions its use not only as a curative method but also as a pre- and postoperative help. The benefit of this therapy in noninflammatory conditions is stated. He feels that in some instances short wave treatment of the pituitary gland can be useful in various types of amenorrhea or irregularities of the menstrual cycle. A very good presentation of this form of treatment in gynecologic disorders.

—*Philip F. Williams*

Dr. Runge presents a second edition of his monograph on *Hemorrhage and Leucorrhea.*[14] The early appearance of this edition has been considered necessary on account of the rapid developments in endocrinology. These advances have been incorporated in the text of the different chapters where such inclusions were pertinent. Runge not only refers to biologic therapy in the different chapters but adds three sections on follicular hormones, corpus-luteum hormones and the gonadotropic hormones, differentiating their qualities and suggesting caution in their therapeutic uses in the disorders of the menstrual cycle. In his discussion he makes a clear differentiation of substitution therapy and stimulation therapy as well as between the estradiol-benzoate and estrin.

There is an excellent short section on the various types of leucorrhea, functional and infective. Runge favors the Sturmdorf operation for the leucorrhea of chronic cervical origin.

—*Philip F. Williams*

Da Costa's *Lectures on Clinical Obstetrics*[15] form a large volume of 623 pages. The lectures are very complete, show a due spirit of conservatism, and include the modern additions to obstetrics.

The appearance of the book both as to paper and illustrations would not pass muster in this country. The illustrations, where they show position of fetus, are at least understandable, but when attempts are made to show skin and bone lesions of syphilis, they fail completely.

—*R. T. Frank*

Maternal Care, Marriage, etc.

This small volume, *Maternal Care, Complications*[16] appears as a supplementary text to the treatises on Maternal Care published by the American Committee on Maternal Welfare. The table of contents lists the Toxemias of Pregnancy, Obstetric Hemorrhage, and Puerperal Infections.

These subjects have been correlated by the entire committee as an editorial board, for the benefit, particularly, of the general practitioner who includes obstetrics in his work. It is believed and hoped that this presentation of such important subjects will be a decided help to those engaged in the practice of obstetrics.

—*Philip F. Williams*

Season of Birth[17] represents the continuation of a study begun several years ago by Dr. Huntington on the effect of the time of birth on mental and physical development. The study described in this book examines millions of births in order

[14]**Blutung und Fluor.** Von Professor Dr. Hans Runge, Universitaets-Frauenklinik, Heidelberg. Third improved edition, with 17 illustrations. Theodor Steinkopff, Dresden, 1938.

[15]**Licoes de Clinica Obstetrica.** Par Clovis Correa da Costa, chefe do Servicio de Ginecologia do Hospital da Fundacao Gaffree-Guinle. Livraria Moura, Rio de Janeiro, 1938.

[16]**Maternal Care, Complications.** Prepared under editorship of Dr. Fred L. Adair, and approved by the American Committee on Maternal Welfare, Inc. University of Chicago Press, 1938.

[17]**Season of Birth.** Its Relation to Human Abilities. By Ellsworth Huntington, Yale University. 473 pages with 104 figures. John Wiley & Sons, Inc. New York, 1938.

to determine the reasons for their seasonal fluctuations and the degree to which births at different seasons vary in quality. Dr. Huntington concludes that man has two different optima of temperature—physical and mental, a relic of the glacial period. The second main result of his study seems to give evidence that man inherits an extremely complex and delicate adjustment to climate and weather. He considers that adjustment hinges on four conditions surrounding conception and birth, the dangers of summer heat to the newborn and the curious relation of low temperature to those of unusual mental ability as well as to the time of their conception.

He attempts to show through statistical tables and deductions therefrom, types of climatic influences, a study not only by geographical variations but by sex ratios, birth incidence, the effect of social custom, marriage habits, agricultural and seasonal migrations. He considers the relation of seasons of births by world trend as well as local and political units in the United States and other countries.

Terminally, he proposes that our new knowledge as to season of birth can be of practical use only if we use it in one of two ways, first: by changing the present seasonal distribution of births, and second: to discover the exact conditions which make certain seasons favorable in certain societies and countries and then to take steps to create those conditions at other seasons of the year. Such a bold eugenic plan will probably not be employed for many generations.

—*Philip F. Williams*

Biography of the Unborn[18] by Margaret Shea Gilbert, an account of the development of the human body, represents, in the opinion of a jury selected by the publishers, "the best book on a scientific subject for general reading."

The book is intended for lay reading and records in simple, concise, understandable style the chronologic changes which take place in the development of the human body before birth, as well as a chapter on the physiology of the exit of the fetus from the mother. A chapter on twinning and one on variations in development are included. The easy style, factually clear text and illustrations should render the book thoroughly suitable for the lay audience for which it is intended.

—*Philip F. Williams*

In this somewhat unusual volume, *The Man Takes a Wife*,[19] Dr. Wile presents a study of man's problems in and through marriage from the standpoint of normal relationships of a sexual, social, and domestic character. Much has been written upon the feminine life cycle from both the normal and pathologic viewpoint, but here for the first time the practical phases of male life are discussed in the hope that men may be enabled to understand themselves better and that the book may serve at the same time as a guide to women in the mutual problems of marital relation.

Dr. Wile discusses the changing social order occasioned by the transformations in recent years in society as a whole. He analyzes the mental and biologic impulses which lead to courtship and marriage, and considers the various readjustments which men must make in marriage and parenthood. He suggests ways and means to diminish the rising divorce rate. The problems of reproduction, and the husband's position and attitude toward them, include the consideration of limitation of family and pregnancy. The book continues through father to child relation, and the position of the father of the family circle.

Dr. Wile develops the subject of adolescence in the offspring and its treatment by parents. The trials and problems of middle age and family life and the necessary marital readjustments of the male climacteric offer a sound interpretation of the peak and decline of man's virility.

This clear discussion of the daily realities of a man's life in the family circle should fulfill the hitherto unsupplied discussion of marriage problems from the masculine angle, and can be read with profit by both husband and wife.

—*Philip F. Williams*

[18] **Biography of the Unborn.** By Margaret Shea Gilbert. Illustrated. 132 pages. The Williams and Wilkins Company, Baltimore, 1928.

[19] **The Man Takes a Wife.** A Study of Man's Problems in and through Marriage. By Ira S. Wile, M.D. 277 pages. Greenberg Publishers, Inc. New York, 1927.

Médecine et Mariage[20] is the product of the Lyons group which publishes bulletins dealing with medical, philosophic and biologic subjects. This present volume deals with a medical problem from philosophic and clerical as well as medical aspects.

Celibacy, marriage, the problems which arise from both conditions in both the normal and abnormal individuals are taken up. Throughout there is a plea for a higher motive than merely sex satisfaction or a race urge to populate the state. It is said that contraception has a bad effect on both man and woman. This book appears to have been written mainly with the object of clarifying the doubts of lay believers.

—*R. T. Frank*

Men Past Forty[21] by Niemoeller (by the way, he is not a physician) is a well-written brochure intended for the educated layman and dealing with the subject of impotence. The tone of this book is high. Most of the information contained appears fully authenticated. The author draws a rather dark picture of the prevalence of impotence in one form or another after the age of forty.

The sole blot on the "scutcheon" is the list of aphrodisiacs supplied towards the end of the book; it is true, with the recommendation that they should not be employed except under the guidance of the physician. This list, which contains not only the names of the products but the firms manufacturing them, on the whole does not meet any of the criteria which a physician would demand before recommending such a volume to his patients.

—*R. T. Frank*

This little pamphlet, *Technique of Contraception*,[22] takes up the technique of various contraceptive measures, including that practice known as the "safe" period method. Matsner concludes that the method of choice at the present time is the combination of a mechanical barrier and a spermicidal agent.

—*Philip F. Williams*

Privately printed to promote the aims of the Free Speech League, *A Challenge to Sex Censor* by Theodore Schroeder[23] discusses his personal ideas on the definition of obscenity as developed by himself and those, especially of the judiciary, who have differed in their interpretation and definition from him. The author states that "if lawyers or judges had combined healthy-mindedness, with some psychological intelligence, they would long ago have discovered that they were no longer able to consider the issue of obscenity, as one of art, morals or religion." Whether or not obscenity may be regarded as subjective or entirely objective will likely long remain a moot point. Probably the conflict between Puritanism and broad-mindedness will continue for some time.

Those who are interested in breaking down some remaining barriers may find, to them, plausible arguments in this confused Freudian presentation.

—*Philip F. Williams*

Endocrine Glands: Vitamins

The Pituitary Gland[24] is a symposium covering an investigation of the most recent advances. It was presented before the Association for Research in Mental and Nervous Diseases at their 1936 meeting. A large number of well-known investigators and clinicians took part in this symposium. The entire volume covers 764 pages.

[20] **Médecine et Mariage.** Par R. Biot, H. Bon, F. Dumarest, J. Gate, J. Gaucherand, E. Lancrenon, M. Péhu, W. Riese, G. Thibon, H. Vignes. Groupe Lyonnais D'Études Médicales Philosophiques et Biologiques. 254 pages. Librairie Lavandier, Lyon, France.

[21] **Men Past Forty.** By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 154 pages. Harvest House, New York, 1938.

[22] **The Technique of Contraception.** An Outline. By Eric M. Matsner, M.D. Foreword by Frederick C. Holden, M.D. Fourth edition, illustrated, 50 pages. The Williams & Wilkins Company, Baltimore, 1938.

[23] **A Challenge to Sex Censors.** By Theodore Schroeder. Privately printed. New York City, 1938.

[24] **The Pituitary Gland.** An Investigation of the Most Recent Advances. Proceedings of the Association for Research in Mental and Nervous Diseases, December 28 and 29, 1936. Williams and Wilkins Company, Baltimore, 1938.

Like all such joint presentations, it varies greatly in the value of the different contributions. Section I, which deals with the anatomy of the pituitary, is particularly valuable and has engaged the attention of Tilney, Wislocki, A. Severinghaus, and Rioch. This covers both the gross and microscopic anatomy as well as the blood supply of the organ.

Section II deals with the physiology and is more than double the size of the previous section. We will mention only a few contributors: Evans, Hisaw and Fevold, Collip, Engle, Philip Smith, Fluhmann, and Riddle. From this it will become apparent that every phase of physiology has been dealt with.

Section III covers general considerations mainly from the point of view of the clinician. This is, as can be foreseen, the most uneven of the sections. The study of the glands of internal secretion is still in such a fluid state that almost any hypothesis may be discussed and theories changed from day to day.

This contribution, as a whole, is of importance in regard to some of its contents as a source book, in others merely as a temporary point of view. It is well worth studying.

—*R. T. Frank*

Oppenauer and Dessau[25] from Laqueur's Pharmacological Laboratory have sent a reprint which is part of the Tabulae Biologicae, Volume 15. These very valuable and easily referred to tables cover the sources, methods of identification and constitution of the sex hormones, including the international units, tests and all derivatives so far obtained. Included are the male, the female and the corpus luteum hormones. The tables give references by number to the appended literature.

Dessau takes up the biologic action of these hormones as seen in plants, cold- and warm-blooded animals. The effect on the metabolism, circulation, sex, primary and secondary sex organs as well as on the other glands of internal secretion are given, also those noted in pregnancy. This is a valuable contribution particularly for those interested in looking up the literature.

—*R. T. Frank*

Miss Jennie Gregory has written a book on the *A B C of the Vitamins*[26] which corresponds in its method of presentation to the *A B C of the Endocrines.*

While this is a clear and excellent presentation, it has not lent itself as dramatically to the pictorial form as the previous book. Vitamin A, the epithelial protective agent; B_1 and B_2 for beriberi and pellagra; the antiscorbutic factor C; the calcifying vitamin D; the sex vitamin E, are depicted in numerous charts. A chapter on experimental methods and the general relationship of vitamins and nutrition conclude this very interesting, useful little monograph.

—*R. T. Frank*

Die Vitamine in der Chirurgie[27] is one of the short monographs published in *Vorträge aus der Praktischen Chirurgie.* It contains a clear and understandable summary of what we know about vitamins A, C, D, and B_1. Emphasis is placed upon the closer relationship between hormones, vitamins, and ferments. A lack of vitamin may be due not to deficiency of nutritive intake, but to excess requirements under particular conditions, excess excretion or excess utilization. It is known that there is an increased loss of vitamin C, ascorbic acid, following anesthesia; hypovitaminoses occur from inflammation and in cancer patients. According to the author, vitamin A protects the liver against hyperthyroid action and makes the use of codeine preoperatively unnecessary.

—*R. T. Frank*

[25] **Sexual Hormone.** By R. Oppenauer and F. Dessau. 121 pages. Uitgeverij Dr. W. Junk, Den Haag, 1938.

[26] **A B C of the Vitamins.** A Survey in Charts. By Jennie Gregory, M.S. Foreword by Walter H. Eddy, professor of physiologic chemistry, Teachers College, Columbia University. Williams & Wilkins Company, Baltimore, 1938.

[27] **Die Vitamine in der Chirurgie.** Von Professor Dr. Erich Schneider, Chirurgische Univ. Klinik, Freiburg i.B. Verlag von Ferdinand Enke, Stuttgart, 1938.

The Vitamins and Their Clinical Applications[28] by Stepp, Kuehnau, and Schroeder has been translated by Dr. Herman A. H. Bouman. It is published by the Vitamin Products Company. The German publication appeared in 1936.

The contents of this book as far as it covers the knowledge acquired on the vitamins, particularly the chemistry and physiology, is of general interest. The translation in places is cumbersome. Much of general interest is found in these pages and considerable applies particularly to obstetrics and gynecology.

—*R. T. Frank*

Surgery

The Therapeutic Problem in Bowel Obstructions[29] is an elaboration of the essay which received the Gross Prize award of the Philadelphia Academy of Surgery. It is a most important contribution to the subject because it gives not only a full survey of the experiments on animals, dealing with the subject of intestinal obstruction, but likewise a detailed account of the clinical features and methods of therapy to be used on patients.

One of the greatest advances has been the prolonged conservative decompression in the treatment of bowel obstruction by means of the modified Levin duodenal tube with continuous suction. This method of treatment is now so standard that its value requires no discussion. Every surgeon will benefit by reading this monograph and every physician will find it worth while to study it. The book is fully illustrated by numerous line drawings and innumerable well-reproduced x-ray plates.

—*R. T. Frank*

Spinal Anesthesia[30] by Maxson is a textbook covering the entire subject in great detail. There is a foreword by W. Wayne Babcock who has been one of the main sponsors of spinal anesthesia in this country and whose experience now reaches some forty thousand cases. Maxson gives the historical basis of spinal anesthesia which was introduced by August Bier. He likewise speaks of the trip made to the United States by Jonnesco in 1910 which many of the surgeons still remember.

The entire subject is covered, if anything, in too great detail. The chemistry of the drugs which have been and are employed, is entered into. The innumerable variations in technique are fully described, including a discussion of hypo- and hyperbaric solutions in which the gravitational effects are most marked. The anatomy, indications, dangers, recovery of broken needles and such divers topics are included.

The author personally uses gravity control, premedication including barbiturate, morphine and atropine. He uses ephedrine prophylactically and novocaine crystals without barbotage.

His point of view is extremely conservative, particularly in selection of cases and makes no exaggerated claims for this method of anesthesia. The book is excellent for reference and for study both for those desiring to learn the technique as well as those who are practicing it.

—*R. T. Frank*

Friedländer in his *Therapy of Thrombosis*[31] based his study largely on the compression bandage treatment first proposed by Heinrich Fischer. This short monograph details the author's experience on 2,500 patients, mainly those of the Wiener

[28]**The Vitamins and Their Clinical Applications.** A Brief Manual. By Professor Dr. W. Stepp, Director of I. med. Klinik, University of Munich, Dozent Dr. Kuehnau, in Wiesbaden, and Dr. H. Schroeder, Associate, I. med. Klinik, Munich. Translated by Dr. Herman A. H. Bouman, Minneapolis, Minn. The Vitamin Products Company, Milwaukee, Wis., 1938.

[29]**The Therapeutic Problem in Bowel Obstructions.** By Owen H. Wangensteen, M.D., Ph.D., Professor of Surgery, University of Minnesota, etc. 90 illustrations, 360 pages. Charles C. Thomas, Springfield, Ill., 1937.

[30]**Spinal Anesthesia.** By Louis H. Maxson, A.B., M.D. Practicing Specialist in Anesthetics; Former Chief Anesthetist, Harborview (King County) Hospital, Seattle, Washington. Foreword by W. Wayne Babcock, M.D., LL.D., F.A.C.S. Professor of Surgery, Temple University School of Medicine. With 69 illustrations, 409 pages. J. B. Lippincott Co., Philadelphia, 1938.

[31]**Die Therapie der Thrombose.** Von Dr. Ernst Friedländer mit 27 Abbildungen im Text. Franz Deuticke, Leipzig und Wien, 1938.

Krankenkasse. He claims to have reduced the average morbidity in individual cases from seventy-five days to six days, without a single embolic death. These patients apparently were mainly cases of phlebitis from varicose veins.

In bed patients the posture should favor unhindered venous circulation. The femur should be at an angle of 45 degrees to the hip, the leg being horizontal. A compression bandage is put from the toes upward and then he starts movements against resistance, performed by the patient himself. Outward rotation of the femur, however, is strictly contraindicated. The patients are gotten out of bed very early. The latest was twenty days postoperative. There were no deaths. The average duration of illness was one week. These results are almost incredibly good and well worth careful study.

—*R. T. Frank*

Volume IV, Part 3, of Peterson's *The Patient and the Weather*[32] deals with organic disease, especially surgical problems. "Superficially it links the patient who may be suffering from an acute abdominal condition to the meteorological environment."

The effect of weather on mass metabolic trends, susceptibility to infection (colds, sore throats), gastric ulcer, are only a few of the subjects trenched upon. Postoperative complications, eclampsia, and even ectopic pregnancy are said to be influenced by the meteorologic environment. A mass of statistics, charts and case histories form the text.

—*R. T. Frank*

In this monograph, *Innere Medizin in der Chirurgie*[33] v. Kress and Kittler discuss the relationship of the important systemic diseases which may be complicated by surgical lesions necessitating operation. They discuss also the complications which may arise in various systems following operation. The first chapter details the preparation for operation of the patient with cardiovascular diseases of various forms, emergencies which may arise during operation and the treatment of the changes in the circulatory apparatus, which may occur postoperatively. There is an excellent chapter on surgery in diabetics, which makes particular reference to preoperative standardization and insulin dosage and postoperative acidosis. In the discussion of surgery on the icteric patient the authors lay stress on the preoperative preparation with vitamins A and C. The respiratory system is considered not only from its intrinsic pathologic physiology complicated by surgery but in addition the authors discuss the different types of postoperative complications, particularly the therapy of postoperative pneumonia and postoperative pulmonary collapse. The final chapter discusses the physiology, pathology, and pre- and postoperative treatment of surgical lesions which are complicated, as in either brain tumor or other nerve lesions, by loss of sleep and the effect of narcosis in the preoperative handling of such conditions.

—*Philip F. Williams*

Miscellaneous

Dr. Donald Mainland of Dalhouse University, Halifax, has written a book which should be valuable to all medical men who write papers based on statistical or other data, as well as to laboratory experimentalists who are not fully familiar with the present statistical ideas. It is called *The Treatment of Clinical and Laboratory Data*.[34]

"The primary object of this book has already been stated—to present ideas and some methods that may help the medical or dental clinician who wishes to benefit from his own observation and from a critical reading of statements made by others."

[32] **The Patient and the Weather.** By William F. Peterson, M.D. Vol. IV, Part 3. Organic Disease—Surgical Problems. Edwards Brothers, Inc., Ann Arbor, Mich., 1938.

[33] **Innere Medizin in der Chirurgie.** Von Dozent Dr. H. Frh. v. Kress, und Dr. W. Kittler, chirurgische Universitaets-Klinik in Muenchen. 114 pages. Ferdinand Enke Verlag, Stuttgart, 1938.

[34] **The Treatment of Clinical and Laboratory Data.** An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By Donald Mainland, Professor of Anatomy, Dalhouse University, Halifax, Nova Scotia, Canada. With 23 text figures. 340 pages. Oliver and Boyd, Edinburgh, 1938.

The average medical writer does not make adequate allowances for chance in all observations and judgments. The author believes that the statistical technique and methods can be grasped in three or four hours of reading. I must confess that it has taken me much longer to run over this book for the first time but that it well warrants careful and repeated study. The use of statistical methods will prevent many brash and unfounded statements from being accepted. The style is clear and the presentation is such that even those who are not mathematically minded will grasp it if they will study it with care.

—*R. T. Frank*

A Textbook of Clinical Pathology[35] edited by Roy R. Kracke has been written by a number of contributors, all of them connected with universities of our South. The work was first undertaken by Dr. Foster M. Johns of Tulane University and was finished at the time of his death in 1936. Since then it has been brought fully up to date. It covers every aspect of clinical pathology. The authors have worked out every detail that the physician requires, beginning with his laboratory equipment, reagents, and methods of technique, including such items as the making and examination of blood smears, venepuncture, blood volume, etc. The diagnostic agglutination tests, clinical chemistry, including liver, urine, and renal function tests are fully described. The examination of sputum, gastric and cerebrospinal fluid, the laboratory tests in syphilis, and, among miscellaneous tests, those for pregnancy, rabies, and allergy are described.

The book is well planned, well edited, well illustrated, and faultlessly gotten out. It should be of real help, particularly for those who only occasionally perform such laboratory tests, although it is full enough to be of real use to the professional laboratory worker.

—*R. T. Frank*

A Biological Approach to the Problem of Abnormal Behavior[36] presents an alternative to psychoanalysis. The author feels that neither the failure to satisfy the sex hunger (Freud) nor the failure to satisfy the hunger for approval (Adler) is a fact of sufficient importance to give a basis of a scientific foundation upon which psychopathology can be built. In other words, in contrast to the Freudian, Adlerian, Jungian motivistic basis for abnormal behavior, he predicates a strictly mechanistic (physiologic) basis and upon this mechanistic basis he tries to lay the foundation of psychology and psychopathology.

He says "there is no real distinction between our normal mental processes and those which we are accustomed to speak of as abnormal." Normal psychology must be physiologic and abnormal psychology must rest upon normal psychology. During the course of twenty years he has studied particularly fear, pain, anger, pleasure, and laughter. He has assembled many data and accumulated them to build up his theory. To the author's way of thinking, psychoanalysis stands today as the chief obstacle to progress in the study of the abnormal.

Behavior is due to a highly complicated anatomic mechanism (sense organs, nervous systems, muscles, endocrine glands). Defects and limitations of this mechanism of behavior and not unconscious motives and desires produce abnormal thoughts, feelings, and actions. In the present volume of 459 pages he discusses psychophysiology and pathology, leaving what he calls psycho-orthology or the treatment of these diseases, for a subsequent volume. He is willing to concede the physical mechanism and only that. The state of consciousness is an epiphenomenon or bi-product of physiologic reactions that give rise to our actions. He discusses nonadjustment and maladjustment. He claims it is not the details of formulation presented that are important but the principles which have been followed in their construction.

[35]**Textbook of Clinical Pathology.** Edited by Roy R. Kracke, M.D., Professor of Pathology, Bacteriology and Laboratory Diagnosis, Emory University, etc. With the assistance of twelve outstanding contributors. Illustrated, 567 pages. William Wood and Company Division, Williams and Wilkins Company, Baltimore, 1938.

[36]**A Biological Approach to the Problem of Abnormal Behavior.** By Milton Harrington, M.D., Psychiatrist, Institution for Male Defective Delinquents, Napanoch, N. Y. 459 pages. Distributed by The Science Press Printing Company, Lancaster, Pa., 1938.

He emphasizes three differences from psychoanalysis. First, the approach. Normal behavior is merely the behavior suited to our needs. Second, the basic concept; every phenomenon results from some action or change acting upon an anatomic structure. Third, evidence, factual or material, which has shaped his theory to fit the facts and not vice versa as he implies is the case in psychoanalysis.

This is a very well-written, carefully thought-out book which without question will arouse interest, discussion and possibly controversy, particularly in neurologic circles. But it is of equal interest to every medical man.

—*R. T. Frank*

The Troubled Mind[37] is a study of nervous and mental illnesses which will interest the medical man, the sociologist, and the educated lay reader. It is a mellow and not too technical exposition of the forms which diseases of the mind assume. The text covers fixed idea and reaction, psychoneuroses (manifestations, nature and causes), traumatic hysteria, inhibitions and mental diseases. Innumerable clinical histories illustrate the exposition.

The author warns that the aggressive psychopath who finds his way into public life may lead the way to social unrest, war and revolution. He likewise points out the futility of committing the psychopathic criminal to variable periods of imprisonment according to the gravity of his crime. If the disease cannot be cured he should be committed permanently.

—*R. T. Frank*

A History of Women in Medicine[38] is a fascinating discussion of medical women from the earliest times to the beginning of the nineteenth century. The author, Kate Campbell Hurd-Mead, publishes this as the first volume, the second to cover the nineteenth century up to the present time. Although well documented, the book is written in such a fashion that it can be read with equal pleasure by the profession or the laity. It takes up not only medical women, but the customs of the times, male physicians if these were the teachers of the females, lay women who practiced medicine, particularly in the middle ages, and the whole aspects of each century, including not only the customs, living conditions, but the situation of women as a whole. In addition the lives of female practitioners are discussed in detail.

Anyone interested in the history of medicine, in fact in history as a whole, will read this book with a great deal of enjoyment and profit. It is to be hoped that the author will be able to carry out her purpose of publishing a second volume which will bring her up to the present time.

—*R. T. Frank*

The brilliant career in medical history of Dr. Fielding H. Garrison forms the subject of this biography,[39] and the selected letters of his correspondence. Dr. Garrison may be regarded as a pioneer in the development of American Medical History, and he made this subject his life work. While the *Index Medicus*, in recent years known as the *Quarterly Cumulative Index*, is a godsend to the present-day researchers and medical literateurs, there can be no doubt but that Dr. Garrison's labors on these publications will be held in a continuously increasing appreciation by the scholars of coming generations. Chapters on the story of his life depict his work as a biographer and teacher, his intense love of music, his relationship with his fellow-men and his army colleagues. The many selected letters from his correspondence reveal intimately his many interests. The book closes with a bibliography of his writings and the various appendices expressing further his character and activities.

—*Philip F. Williams*

[37] **The Troubled Mind.** A Study of Nervous and Mental Illnesses. By C. S. Bluemel, M.A., M.D., F.A.C.P., M.R.C.S. (Eng.). 520 pages. Williams & Wilkin Co., Baltimore, 1938.

[38] **A History of Women in Medicine.** From the Earliest Times to the Beginning of the Nineteenth Century. By Kate Campbell Hurd-Mead, M.D. Illustrated. 569 pages. The Haddam Press, Haddam, Conn., 1938.

[39] **Life and Letters of Fielding H. Garrison.** By Solomon R. Kagan, M.D. With an Introduction by Professor James J. Walsh. 287 pages. The Medico-Historical Press, Boston, 1938.

In his *Adventures in Respiration*[40] Dr. Henderson discusses the modes of asphyxiation and methods of resuscitation. Dr. Henderson pioneered many years ago with Dr. Howard W. Haggard in the treatment of carbon monoxide poisoning by inhalation of carbon dioxide diluted with oxygen. The practical aspect of this method of revival is current in the practice of all obstetricians in the treatment of asphyxiation and narcotized newborn.

For many years Dr. Henderson's theory regarding the relationship of acapnia to postanesthetic and physical depressions was not generally accepted, but today, as he states in his introduction, the acapnia theory has won its way into surgery, as manifested by the carbon dioxide cylinders in every operating room. In this discussion of asphyxia and resuscitation the story is told in simple language as an adventure which Dr. Henderson has experienced. After recounting the theories of the physiology and pathology of carbon dioxide deficiency, acapnia, carbon monoxide asphyxia, and the resuscitation therefrom, a chapter is devoted to the gases of peace and war. Here the horror of one is offset by the spectacular rescues of the resuscitation teams in commercial and civil life.

Of particular interest to the obstetrician should be Chapters 9, 10, and 11, "How Breathing Begins at Birth," "Asphyxia of the Newborn" and "Resuscitation of the Newborn." Dr. Henderson believes that the function of muscle tonus, deficient in the fetus but present at birth in the normal infant is the answer to the question, "Why does the baby begin to breathe at birth?" He states that even days may be required for complete dilatation of the lungs in infants judged to be wholly normal at birth.

He recounts the factors tending toward the production of asphyxia in the newborn and describes four types of asphyxia. He regards the long "narcotized baby" as due to the excessive use of narcotics and hypnotics in present-day American obstetrics. The various measures used in the resuscitation of the newborn are described. The value of oxygen and carbon dioxide and oxygen by the inhalational treatment are stressed, and the objections to the use of these gases are fully answered.

Remaining chapters in the book discuss such other types of asphyxia and alterations in respiration as may be found in postoperative depression, pneumonia, and circulatory failures.

The book, a succinct and easily read résumé of the important researches of Dr. Henderson in this most important subject, merits reading by all whose work comes in contact with the problems of asphyxia and anesthesia.

—*Philip F. Williams*

This *Textbook of Anatomy and Physiology*[41] may well be considered to have become a standard in nursing education in having reached a tenth edition. Its life span has now attained forty-four years.

In this new edition an effort has been made through the deletion of obsolete material to keep the book of the same general size as heretofore. Recently established work on physiology, vitamins, endocrine secretion, new work on nervous activity and the recent studies of the kidney have been incorporated.

It is stated in the preface of the previous edition that the authors had aimed to include the material outlined in the course in Anatomy and Physiology in the Curriculum published by the National League of Nursing Education. The idea of the comprehensiveness of such a curriculum is afforded through a perusal of the 600 odd pages comprising the subjects of anatomy and physiology discussed.

—*Philip F. Williams*

[40]**Adventures in Respiration.** Modes of Asphyxiation and Methods of Resuscitation. By Yandell Henderson. Illustrated, 316 pages. Williams and Wilkins Company, Baltimore, 1938.

[41]**Textbook of Anatomy and Physiology.** By Diana Clifford Kimber, Carolyn E. Gray, A.M., R.N., and Caroline E. Stackpole, A.M., Associate in Biology, Teachers College, Columbia University. Tenth edition, revised and rewritten. 276 illustrations, 643 pages. The Macmillan Company, New York, 1938.

Hemorrhoids[42] by Marion C. Pruitt is a short monograph on the diagnosis and treatment of this condition. Anatomy and instrumentarium are given in detail. Nupercaine local infiltration anesthesia is preferred. Proper stress is laid upon the importance of accurate diagnosis. The indications for selecting either operation or injection treatment are described. This monograph is short, clear, and well illustrated.

—R. T. Frank

In a review of the preceding twelfth edition of *Osler's Principles and Practice of Medicine,*[43] only two years ago, we gave expression to the hope that the untimely demise of its then editor, Thomas McCrea, would not prevent the presentation of an equally excellent edition of this popular textbook in the future. As a pupil of Osler, and colleague and friend of McCrea, the editor of this new thirteenth edition, Henry A. Christian, found a welcome opportunity of continuing the medical tradition of this work. Once again the volume has been partly rearranged and rewritten to include all the recent advance, especially in the field of therapeutics. It has been enlarged by approximately 300 pages.

—Hugo Ehrenfest

This volume comprises a complete consideration of *Clinical Roentgenology of the Digestive Tract.*[44] Starting with the diseases of the esophagus the succeeding chapters deal respectively with stomach, duodenum, small bowel, colon, etc. The various types of hernia are included, as well as the diseases of the gallbladder and pancreas. Special chapters are devoted to omental, retroperitoneal and mesenteric tumors, peritonitis, pernicious anemia and to the various functional disturbances of the gastrointestinal tract.

The important feature of practically all of the 20 chapters is the x-ray demonstration of the underlying pathology. The roentgen examinations in general follow accepted routine procedures, the results being depicted in excellent cuts and illustrations. The arrangement of references at the end of the chapters is convenient, the index seemingly complete. All through the volume the descriptions of symptoms and findings are concise but clear.

This new contribution to roentgen literature must be welcomed chiefly on account of its completeness and its value for ready reference.

—Paul C. Schnoebelen

The task of keeping *The American Illustrated Medical Dictionary*[45] abreast with progress must be formidable. The appearance of newly coined terms in modern medical literature progresses with astonishing rapidity, and thus 3,000 new words had to be defined in this edition, requiring 60 additional pages.

The gynecologist will be surprised to learn that in this edition, as far as we know for the first time in any dictionary, a definition of that widely used term "climacterium" appears. A comparison of definitions of other common gynecologic terms in various dictionaries clearly proves the need for more precise gynecologic terminology.

—Hugo Ehrenfest

[42] **Hemorrhoids.** By Marion C. Pruitt, M.D., Atlanta, Georgia, President, American Proctologic Society, Associate in Surgery, Emory University School of Medicine, etc. With 73 illustrations, including 7 in color, 170 pages. The C. V. Mosby Company, St. Louis, 1938.

[43] **Osler's Principles and Practice of Medicine.** Designed for the Use of Practitioners and Students of Medicine. Thirteenth edition. Revised by Henry A. Christian, Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief of Peter Bent Brigham Hospital, Boston. 1,450 pages. D. Appleton-Century Company, New York, 1938.

[44] **Clinical Roentgenology of the Digestive Tract.** By Maurice Feldman, M.D., Assistant Professor of Gastroenterology, University of Maryland, Baltimore, etc. With a Foreword by Julius Friedenwald, A.M., M.D. 358 illustrations and 1,011 pages. William Wood & Co., Baltimore, Md., 1938.

[45] **The American Illustrated Medical Dictionary.** By W. A. Newman Dorland, A.M., M.D., F.A.C.S. Eighteenth edition, revised and enlarged, with 912 illustrations, including 283 portraits, 1667 pages. With the collaboration of E. C. Miller, M.D., Medical College of Virginia. W. B. Saunders Company, Philadelphia, 1938.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Menstruation

Lass, Smelser and Kurzrok: Studies Relating to Time of Human Ovulation, Endocrinology 23: 43, 1938.

Forty-seven women studied through their post-partum period had 194 fairly regular cycles. One hundred and six cycles (55 per cent) were anovulatory or sterile in character, and the bleeding was not true menstruation, since it did not come from a premenstrual endometrium. Eighty-two cycles (45 per cent) were ovulatory in character, hence fertile, and the bleeding represented true menstruation.

J. THORNWELL WITHERSPOON

Hisao, I.: On the Symptoms of Ovulation, Japanese J. Obst. & Gynec. 21: 22, 1938.

The author interrogating a group of nurses and female medical students at the Osaka Medical College for Women came to the conclusion that women can perceive various symptoms which occur during ovulation. The most frequent among them is leucorrhea, but other symptoms are languor, enlargement of the breasts, distention of the lower abdomen, drowsiness, etc. The symptoms appeared in most cases from the twelfth to the sixteenth days before the next flow. In most instances they persisted for about three days. Only 40 per cent of nurses but 70 per cent of the women doctors and medical students noticed such symptoms of ovulation.

J. P. GREENHILL

Duckles, D., and Elvehjem, C. A.: Hemoglobin Studies on College Women with Special Reference to the Effect of Menstruation, J. Lab. & Clin. Med. 22: 607, 1937.

It seems to be generally conceded that there are both daily and hourly fluctuations in hemoglobin and that these are more pronounced in women than in men. Whether or not the variation in women can be attributed in part to menstruation, causing an instability of the hematopoietic system and increased physiologic demands for iron, is unknown. In various series reported, some investigators have concluded that increases and decreases in the hemoglobin during the menstrual period were no different from those in the intermenstrual period, while others have reported a blood-destroying activity in women coincident with menstruation.

In the present small series of 7 college women, varying in age from 20 to 27 years, hemoglobin determinations were made daily and in some cases hourly for a period of 52 days covering approximately 2 menstrual cycles for each subject. The authors state that these 7 subjects were all healthy although one was slightly anemic and one was diabetic. All, however, were in a good state of nutrition. The specimens were obtained from the finger tips, the Newcomer method was used and compared with a carefully standardized disc in a colorimeter. The results were as follows: The average hemoglobin for the women in this series is approximately 14 gm. per 100 c.c. of blood and shows daily variations ranging from 13 to 15 gm. Hourly fluctuations in hemoglobin occur which are not consistently

comparable at corresponding hours on different days. The hourly variations are as marked during the intermenstrual period as during the menstrual period. There is usually a diminution in the hemoglobin during menstruation, the amount varying considerably with different individals. During the postmenstrual phase of the cycle, there tends to be a rise in hemoglobin which continues to increase slightly during the intermenstrual phase.

W. B. SERBIN

Bokelmann, O.: Blood Changes in the Menstrual Cycle, Arch. f. Gynäk. 164: 597, 1937.

There is a definite decrease in both erythrocytes and hemoglobin content during menstruation. During the premenstrual and postmenstrual periods both are increased. The drop during menses is not due to a thinning or dilution of the blood nor to the blood loss. There is also a decrease in thrombocytes during the menstrual phase. The reticulocytes increase during the premenstrual, menstrual, and postmenstrual phases. There is also an increase in bleeding time during the menstrual phase. No definite leucocytic changes could be determined.

RALPH A. REIS

Gebert, Willy: Capillary Function and Menstruation, Klin. Wchnschr. 15: 828, 1936.

Gebert discusses the various circulatory changes which are found as regular accompaniments of the menstrual cycle such as the premenstrual migraine, premenstrual rise in blood pressure and vicarious menstruation, etc. An attempt was made to study the capillary changes during the menstrual cycle, as it seemed these changes might be important in the understanding of premenstrual migraine and the various types of intracranial bleedings which accompany menstruation.

He therefore investigated the changes in the dermographic latent period and found that capillary function is directly influenced by the various changes associated with the menstrual cycle. There is a definite decrease of the dermographic latent period during the immediate premenstrual days which is followed by a marked rise which reaches its peak with the onset of the menstrual flow. Following this peak there is a rapid falling off until the latent period reaches the normal level again. This occurs as the menstrual flow ends. This premenstrual rise must be due to a spastic condition of the capillary bed.

RALPH A. REIS

Mazer, Charles, Israel, Leon, and Kacher, Leon: Pseudomenstruation in the Human Female, Surg. Gynec. Obst. 65: 30, 1937.

Cyclic uterine bleeding, clinically indistinguishable from a normal menstrual flow, but coming from an endometrium totally lacking the usual secretory changes, occurs in 30 per cent of sterile women who present no abnormality.

The condition is rarely encountered in fertile or potentially fertile women.

The condition may be due to failure of ovulation, a developmental or acquired lack of responsiveness of the uterus to a normal ovarian activity or to a quantitative or qualitative disharmony between the two ovarian hormones, estrin and progestin.

When the diagnosis is based on endometrial findings alone, the term "pseudomenstruation" is preferable to "anovular menstruation" because the presence of the latter cannot be proved without concomitant study of the ovaries.

WM. C. HENSKE

Gillman, Joseph: Experimental Studies on the Menstrual Cycle of the Baboon, South African J. M. Sc. 2: 156, 1937.

Hartman in 1932 reported that repeated laparotomies and manipulation of the ovaries do not apparently interfere with the course of the menstrual cycle in the *Macacus rhesus*.

Gillman showed in 1935 that both transient and prolonged emotional stimuli do affect the menstrual rhythm in the baboon. In this paper he proves that in the baboon laparotomy and simple examination of the ovaries as well affect the menstrual cycle.

The author concludes that in the baboon, when the ovaries are manipulated near the middle of the cycle, the perineal measurements decrease progressively until the fifth or seventh day after the operation and then increase rapidly. The stages of perineal rest and deturgescence are unaffected. No menstrual bleeding supervenes at the end of the initial drop of the perineum. Unilateral ovariectomy in a young baboon, with short and irregular cycles, results in a development of a normal adult type of rhythm at the end of the third cycle following the operation. Hysterectomy does not permanently affect the perineal rhythm.

F. L. ADAIR AND J. A. HAUGEN

Miller, Arthur G.: The Fertile Period in Practice, Surg. Gynec. Obst. 66: 723, 1938.

A five-year clinical study of the fertile and sterile periods of women has been made. This study quite definitely points out the value of accurate menstrual records as an early diagnostic aid of abnormal female sex organ function. It also shows that ovulation has a definite time relationship to the next succeeding menstruation, and indicates that the time between ovulation and the next menstruation is a matter of fourteen days. This interval does not change with change in rhythm.

The regularity, duration, and character of the menstrual periods are the chief signs of normal or abnormal female sex organ function. Barring accident or disease the menstrual cycle of a normal woman varies continually between a certain maximum and minimum number of days.

That there are definite periods of physiologic fertility and sterility in the menstrual cycles of normal women appears to be a definitely established biologic law.

The fundamental scientific basis of the fertile period procedure is sound and reliable. The procedure offers to mankind, when it is supervised by a physician, a simple, dependable, and physiologic method for conception control.

In the author's clinic every menstruating woman is told of the importance of an accurate menstrual record and is given a suitable card on which to record the dates. Every recently confined woman is instructed as to the importance of spacing pregnancies.

WILLIAM C. HENSKE

Mommsen, H., and Sachs, F.: The Dietetic Influence of Fermentation Arresting Substances Produced During Menstruation, München. med. Wchnschr. 84: 208, 1937.

By means of the method described by Mommsen, the woman's blood is examined during two successive menstrual periods for substances which impede fermentation. The following is thereby established: (1) The inhibiting substance in yeast fermentation of dextrose mounts gradually in the premenstrual phase of the cycle, reaches its maximum shortly before bleeding begins, and vanishes rapidly from the blood with occurrence of the flow. (2) The curve representing the inhibiting substances is higher when based on a high animal protein nourishment than on a vegetable diet. This assertion is based upon examinations of women, who during one menstrual period ate an abundance of meat, and during the following period were fed vegetables and fruit. (3) It has been stated that this inhibitory substance, produced during menstruation, is a derivative of cyclopentano-perhydrophenanthrene. The carbon framework of this substance is found in various potent physiologic and pharmacologic bodies (sterine, sex hormones, heart drugs, neutral saponin).

C. E. PROSHEK

Jenkins, Penelope M., Gunn, Donald L., and Gunn, Alistair L.: Menstrual Periodicity: Statistical Observations on a Large Sample of Normal Cases, J. Obst. & Gynaec. Brit. Emp. 44: 839, 1937.

The authors analyze accurate data compiled from questionnaires and record cards from 770 of 852 women who cooperated in the study.

They conclude that the term "regular" has no precise meaning in connection with menstruation. No cases were found which did not vary by at least 2.75 days between the longest and shortest intervals within the year.

The average interval between onsets of menstruation was 29 days; the commonest averages lay between 26 and 29 days; 90 per cent of patients had an average interval between 25 and 36 days inclusive; in 3 per cent it was more than 37 days and in 7 per cent less than 25 days.

A progressive decrease in average interval was noted with increasing age, amounting to about one day for each 5 or 6 years.

No relationship to marriage, occupation, season, or lunar references was noted.

The variability of menstrual intervals is discussed with relation to the Knaus-Ogino safe period method of contraception.

SAMUEL D. SOULE

Wollner, Anthony: The Physiology of the Human Cervical Mucosa, Surg. Gynec. Obst. 64: 758, 1937.

There is a distinct menstrual cycle in the cervical mucosa. This structure being under hormonal influence like the endometrium, the intermenstrual phases must be taken into consideration when the histologic findings in the cervix are interpreted. In the premenstrual phase the histologic picture may simulate an inflammatory reaction, and cyst formations may result from hormone action by producing exfoliation of the epithelial lining.

An investigation of the diagnostic possibilities, suggested by the data presented, is now in progress.

WILLIAM C. HENSKE

Burch, John, McClellan, G. S., Johnson, Claud, and Ellison, Eugene: The Diagnosis and Classification of Menstrual Disorders, J. A. M. A. 108: 96, 1937.

Glandular cystic hyperplasia of the endometrium is the result of prolonged continuous secretion of estrogen; it cannot occur in patients whose ovaries contain active corpora lutea. Such an ovarian state is the result of a partial failure of ovarian function. Partial castration as well as partial hypophysectomy in animals led to cystic glandular hypertrophy of the endometrium.

An attempt was made to correlate (in the human being) symptoms of menstrual disorder with the endometrial picture gained by a series of biopsies, but was unsuccessful. No single endometrial picture is characterized by a specific history.

GROVER LIESE

Thorn, George W., Nelson, Katherine R., and Thorn, Doris W.: A Study of the Mechanism of Edema Associated with Menstruation, Endocrinology 22: 163, 1938.

The injection of crystalline preparations of estrone, progesterone, pregnandiol, and testosterone induced the retention of sodium chloride and water in normal dogs. Balance studies in human subjects demonstrated a retention of sodium chloride and water during the intermenstrual as well as the premenstrual phase of the cycle. The onset of menstruation was associated with an increased renal excretion of sodium chloride and water. Normal subjects, in whom no dietary restrictions were imposed, were observed to gain weight during the intermenstrual as well as during the premenstrual phase of the cycle. An increase in appetite and thirst was a striking symptom noted during the premenstrual period. The increase in the secretion of the sex hormones and the increase in appetite and thirst appear to be contributing factors in body weight gain, which occurs during the menstrual cycle.

J. THORNWELL WITHERSPOON

Bernhart: A Case of Hyperemesis of Menstruation, Zentralbl. f. Gynäk. 61: 196, 1937.

Occasional vomiting during menstruation is not uncommon but uncontrollable vomiting is rare. A case of the latter kind is here reported. A thorough examination was made but no cause for the vomiting could be found. On the assumption that the vomiting was hormonal in origin, and in the knowledge that there is a fall in estrogenic hormone content at the time of the menses, the patient was given 10,000 and 50,000 units of estrogenic hormone. The vomiting ceased but recurred. More injections of estrogenic hormone were given until 100,000 units had been administered. This controlled the vomiting.

J. P. GREENHILL

Merriman, B. M.: Endocrine Treatment of Dysmenorrhoea, Malayan M. J. 12: 56, 1937.

Dysmenorrhea is considered as congestive or spasmodic. In the spasmodic type there are two groups: one associated with disorders of uterine structure, and the other with disorders of uterine function. In the former type there is frequently present a myometrial hypoplasia or a prepubescent uterus. In this condition follicular hormone has proved very beneficial in the hands of the author.

Where the uterus is normal in structure, the pain is regarded as due to an abnormality of function or deficient "polarity." In this type the corpus luteum hormone is recommended, as well as in the congestive type, where the pain is premenstrual and is relieved by the onset of bleeding. Corpus luteum injections of 2 mg. twice weekly over the last fourteen days of the premenstruum are given.

F. L. ADAIR AND S. A. PEARL

Leung, N. M.: Dysmenorrhoea Due to Stricture of Ureter, Chinese M. J. 51: 365, 1937.

The author states that if all gynecologic cases would be studied also from the urologic viewpoint, it would be found that a goodly proportion of menstrual pain has a urologic background. Out of 100 cases of chronic ureteral obstruction in women of menstrual age, it was ascertained that 13 had dysmenorrhea caused entirely by the ureteral obstruction, twelve being cured by its removal; also that in 23 cases the urologic symptoms were aggravated at the time of menstruation. He believed that cases of dysmenorrhea should be scrutinized for hints of ureteral pathology before any radical treatment is instituted.

C. O. MALAND

Ford, Frank R., and Guild, Harriet: Precocious Puberty Following Measles, Encephalomyelitis and Epidemic Encephalitis, with a Discussion of the Relation of Intercranial Tumors, Bull. Johns Hopkins Hosp. 60: 192, 1937.

The authors describe two cases of precocious sexual development in young girls following measles, encephalitis, and another case of premature development of the sex organs and of sexual misbehavior in a boy, following epidemic encephalitis.

A survey of the literature seems to indicate that destructive lesions in the region of the pineal body and in the walls of the third ventricle may result directly or indirectly in the syndrome of macrogenitosomia precox. Cases are cited in which this syndrome was associated not only with tumors arising in the region of the pineal body but with tumors of the hypothalamus. The same syndrome is known to follow inflammatory processes, such as meningitis, meningoencephalitis, and epidemic encephalitis.

The information available at present indicates that the pineal body plays no significant role in the production of macrogenitosomia precox, for this gland is quite normal in many cases in which this syndrome is fully developed, and destruction of the pineal body may be followed by no apparent change in the genital organs. The authors have failed to find a single instance in which definite macrogenitosomia precox has been associated with a verified pinealoma.

C. O. MALAND

Siegert, F.: The Climacterium and Its Treatment, Med. Klin. 33: 561, 1937.

In most instances the climacterium is a physiologic and not a pathologic state. Hence treatment during this period should consist of relieving symptoms which annoy a woman. To accomplish this, great consideration must be given to the woman's psyche. Ordinarily when a diagnosis of "climacteric difficulties" is made we think of "ovarian insufficiency—substitution therapy with ovarian hormones." However, this thought process is correct only when there are such disturbances in menstruation as profuse and prolonged bleeding.

It is possible to influence climacteric bleeding, that is, menorrhagia and metrorrhagia, by means of estrogenic hormone. The latter produces proliferation of the endometrium and improves the contractility of the uterus which leads to a rapid expulsion of the functionalis and thus a diminution in the duration of bleeding. However, it is much more difficult to influence glandular cystic hyperplasia of the endometrium by means of corpus luteum hormone. Hence, from the point of view of differential diagnosis it is important to perform a curettement to determine the type of endometrium which is present.

The author believes that the oral administration of estrogenic hormone is as effective as the parenteral route. He points out that not only may the menstrual disturbances but also the other symptoms, many of which are due to a hyperfunction of the thyroid, be overcome by hormones. This can be overcome by iodine preparations.

Climacteric elevation of blood pressure is best influenced by sedatives combined with ovarian hormones. The arthritis which occurs during the change of life may also be helped occasionally by ovarian hormones.

J. P. GREENHILL

Item

American Board of Obstetrics and Gynecology

Application for admission to the Group A, May, 1939, Board examinations must be on file in the Secretary's Office not later than March 15, 1939. The general oral, clinical and pathological examinations for all candidates, Part II Examinations (Groups A and B), will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the Annual Meeting of the American Medical Association. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for re-examination in Part II (Groups A and B), must request such re-examination by writing the Secretary's Office before April 1, 1939. Candidates who are required to take re-examinations must do so before the expiration of three years from the date of their first examination. The annual dinner meeting of the Board, to which all diplomates and candidates are invited, as well as their wives and others interested in the work of the Board, will be held at the Congress Hotel, St. Louis, on Wednesday evening, May 17, following the close of the examinations. Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

American Journal of Obstetrics and Gynecology

VOL. 37 APRIL, 1939 No. 4

American Association of Obstetricians, Gynecologists and Abdominal Surgeons

PRESIDENTIAL ADDRESS*

OBSTETRICS AND GYNECOLOGY AS A UNITED SPECIALTY

PAUL TITUS, M.D., PITTSBURGH, PA.

DURING the past twenty-five or more years, there have been steadily progressive changes in educational standards, and in methods of training in the specialties. For example, practically all except the youngest members of this Association were not able to have the advantages of present-day facilities for intensive training in obstetrics and gynecology, because, until comparatively recently, opportunities for this were so limited in number. Formerly, as most of us recall, one served his general internship as now, but training in obstetrics and gynecology was usually obtained by apprenticeship to a recognized and outstanding specialist. After more or less prolonged assistantship, one was allowed more responsibilities and wider latitude in his work, still under the close supervision of his preceptor. Hospital staff promotions followed gradually, and presently one became recognized, and rightly so, as a trained specialist.

Time has not lessened the value of this type of training in a specialty, and many men are following this course even now. More intensive methods have partly superseded this however, and to this end internships and residencies in the specialties are now being developed to a high degree of efficiency.

By the older method, young men were inevitably influenced by the personal views and medical activities of their preceptors. Lines of

*Presidential address at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, White Sulphur Springs, W. Va., September 23, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

specialization were not sharply drawn. Gynecology was often a small portion of the work of some distinguished surgeon; another might find that gynecology constituted the major portion of his practice with obstetrics filling a minor place, or the reverse might be true. Younger men were prone, naturally, to follow the example of their masters, and thus the traditions were carried on. Many general surgeons whom we know and revere were trained in this manner to include gynecologic surgery in their work and nothing can detract from the brilliance of their performance of this in many instances.

During the past few years, however, multitudes of new discoveries in all fields of medicine have tended to limit the special activities of physicians within fairly sharply defined borders. On this and other accounts, we are obliged to face the facts of changing times and methods. All of us appreciate, as never before, the breadth and importance of the fields of obstetrics and gynecology, while their interrelationship becomes daily more apparent.

The subject chosen for presentation in this address was not singled out in a controversial spirit. Quite the contrary, it was selected for the express purpose of analyzing these definite transitions and trends in the teaching and practice of obstetrics and gynecology, which are becoming more and more widely established on this Continent. I refer particularly to the growing tendency to combine obstetrics and gynecology as a unified specialty in teaching institutions, in hospitals, and other practice. In Europe, this has been a customary and accepted combination for many years. In this country, however, one still hears a certain amount of persistent opposition to the logical suggestion that midwifery bears so close a relationship to diseases of women that they should be taught and practiced together.

By those not favoring this combination, childbearing seems to be regarded as a simple and normal function, which can be adequately supervised by any general practitioner. They grant that obstetrics is one of the most important branches of medicine, but decline to admit that its importance has developed obstetric specialists and the art of obstetric practice to an extent fully equal to that of any other major specialty. Gynecology is viewed by the same commentators as a mere branch of general surgery, free from any particular influence resulting from improvement in obstetric art, even though many gynecologic ailments are directly the result of poor obstetric care.

The more modern conception is that obstetrics with its multitudinous possibilities for trouble constitutes a major branch of medicine, and that diseases peculiar to women are inseparably associated with their childbearing functions. During recent years this idea has steadily gained more general acceptance on this Continent, although it still meets with sufficient antagonism to warrant a thoughtful analysis of the present situation, both pro and con.

TEACHING COMBINATIONS IN NORTH AMERICA

Accordingly, I inflicted another questionnaire on the Deans of the 75 four-year-medical schools approved by the American Medical Asso-

ciation in this country and Canada. Replies were received from 74 Deans, and I gratefully acknowledge my obligation to them for their generous cooperation in this study. So general a response clearly manifests their active interest in this moot question.

These replies show that the teaching of obstetrics and gynecology from a combined chair is carried out in 45 or approximately 60.8 per cent of the approved medical schools of North America. It develops further that 23 or 31 per cent have separate chairs for each, and it is significant that gynecology is combined with general surgery in only 5 or 6.7 per cent of our approved schools. In one school gynecology is divided between the surgical and the obstetric departments.

CURRENT OPINIONS FAVORING UNIFICATION

In contrast to these latter groups, the American Board of Obstetrics and Gynecology and the White House Conference definitely advocate the unification of obstetrics and gynecology for undergraduate and graduate teaching, and for practice.

Two years ago, Dr. Louis E. Phaneuf, in his presidential address before this Association, took for his subject "The Undergraduate Teaching of Gynecology." He discussed many of the points which I have in mind at this moment, but his theme dealt more with undergraduate education than with graduate training in the specialty. He expressed his firm conviction that the ideal way to teach gynecology to the undergraduate was from a combined chair of obstetrics and gynecology. He said that where this was not yet possible "the teacher of obstetrics should have fundamental training in gynecology as the teacher of gynecology should have in obstetrics, if the best results are to be obtained," and he further stated "For purposes of teaching and giving the patient the best care, the department of gynecology in large hospitals should be separated from general surgery and should function as a unit or as a part of a woman's clinic." This is sound logic, and applies equally well to the teaching and training of resident house officers and other graduate students.

Six years ago, Dr. Walter T. Dannreuther chose as the subject for his presidential address before this Association "The Qualifications of the Specialist." He called attention to the fact that the medical profession has been afflicted with numberless irresponsible self-styled specialists. He said, "The term 'specialist' implies that the individual so designated has had superior training and has assimilated knowledge from a multitude of opportunities, and the public is just beginning to display an interest in the qualifications he really possesses and to question his authority for so classifying himself." This summarizes admirably the reasons which caused the twelve major specialties in medicine to organize certifying Boards. As you well know, these Boards investigate carefully the special training and practice of applicants for certification as specialists, and then conduct rigid examinations to ascertain the extent of their special proficiency before granting certificates. As Dr. Dannreuther said, "The chief purposes of our Board (like the others) are not restrictive but educational: to encourage and induce potential

specialists in obstetrics and gynecology to prepare themselves thoroughly, to persuade medical schools and hospitals to provide adequate facilities for special training, and to put the stamp of approval on qualified specialists." He further said, "The departmental integration and fusion of obstetrics and gynecology is not only desirable but highly essential, because the skillful practice of one is dependent upon a thorough knowledge of the other. It must be conceded that the large Frauenkliniks abroad are far better equipped to produce specialists than our own institutions, although the available clinical material is no greater."

From its beginning the American Board of Obstetrics and Gynecology has insisted that a fundamentally thorough knowledge of both branches is essential, regardless of whether a physician elects to practice one or the other, or both. Therefore, the examinations include both subjects, with especial emphasis on this interrelationship.

In this connection it would have been of interest, had it been possible, to inquire into the arrangements in the many general hospitals of this Continent having obstetric and gynecologic departments, because it is in them that many men receive their graduate training in the specialty. Nevertheless, it is likely that the methods provided for undergraduate instruction in the medical schools are a fair index of graduate training facilities, and of practice in general. Each of these schools has its affiliated hospital, and nonteaching hospitals are likely to emulate the example of the others.

COMMENTS ELICITED BY QUESTIONNAIRE

My questionnaire and the comments it elicited developed many interesting facts.

There seems to be no serious argument over the fact that the childbearing function and diseases of women overlap and interlock so closely that there can be no sharp line of demarcation between them. However, in an attempt to divorce the two in one of these teaching institutions, patients with pelvic disorders are still claimed by the surgical division unless their illness is clearly the result of some obstetric experience or calamity. In the latter event they are conceded to the obstetric and gynecologic division, considered in this particular institution as being "combined." Thus a retrodisplacement of the uterus with symptoms in a nulligravida, which is seldom a surgical problem, is viewed as a case for the general surgeon, whereas a similar condition following pregnancy is assigned to the obstetrician-gynecologist.

In still another important teaching institution, in which it is strongly asserted that gynecology is properly a branch of general surgery, assignment of cases is based upon the rule that all women with pelvic disorders who have not previously been patients in the obstetric division are to be admitted to the surgical-gynecologic service. Only if they have ever been patients on the obstetric service may they return to this department for gynecologic treatment. Thus, a woman with an ectopic pregnancy is not an obstetric case unless previously she had been a patient in the obstetrical department. Both services receive and treat cases of ectopic pregnancy according to this ruling. Indeed, they go even

further than this in this hospital. A patient with a fibromyoma or an ovarian cyst applying for admission is likewise questioned as to previous admissions. If she has had a baby or even an abortion treated there at some previous time her tumor becomes mysteriously related to obstetrics, and she is admitted to and operated upon in the maternity division.

At this same institution, the interns, assistant residents, and residents in gynecology may serve periods of time varying from one to four or five years without ever seeing an obstetric case, without any personal insight into the later effects of some of their pelvic surgery when pregnancy occurs, and without any arrangement whereby they may routinely rotate or have exchange services with men from the obstetric division, if they should wish thus to broaden their knowledge.

Is it necessary to reiterate at this point, that both in teaching and in practice an attempt to create a dividing line between obstetrics and gynecology is impossible, and at times becomes almost ridiculous? Furthermore, gynecology does not bear an inseparable and constant relationship to surgery. In a recent publication I took occasion to say, "Gynecology includes not only local or genital diseases of women, but general and associated glandular dysfunctions. By far the greatest bulk of gynecologic practice is nonoperative, and this, too, should serve to controvert the suggestion that this specialty should be considered a subdivision or branch of general surgery. Office treatments of ambulatory patients predominate greatly in numbers and probably in variety of purposes over hospital admissions and major operations for gynecologic disorders."

OPPOSITION TO UNIFICATION

Having expressed some very definite opinions as to the propriety of combining obstetrics and gynecology, it is proper to consider the other side of the question and to examine the arguments offered against such a union.

The first of these is that "The obstetrician-gynecologist cannot cope with emergencies of abdominal surgery as efficiently as can the general surgeon. He must be trained in and practice general surgery in order to be a safe gynecologist in the abdominal cavity." Some of the emergencies mentioned were intestinal obstruction and tumor growths of the gastrointestinal tract, as well as cholecystitis and cholelithiasis. But does this doubt apply to the properly trained obstetrician-gynecologist? It is agreed that a competent gynecologist must have had good training in abdominal surgery even though these emergencies are distinctly a minor part of his work. It should also be remembered that the interrelationship of obstetric matters is by no means a minor, but rather is a constant, part of his gynecologic work, so that training in this is of more importance than an intensive one in general surgery.

It was interesting to note what constituted "adequate training in gynecology" in the opinion of this particular critic, whose own department is a subdivision of general surgery in his school of medicine. He has a small corps of interns and assistant residents, headed by a chief

resident. While his department is rated as a subdivision of surgery, his men are appointed directly to this gynecologic subdivision, do not rotate through or serve in the general surgical department, and receive their entire training in the gynecologic operating rooms and wards. Their training under his direction is no broader or more inclusive, or better suited to fit them for the general surgical emergencies mentioned, than that of any similar but truly gynecologic service combined with obstetrics. Moreover, there is an entire lack of obstetric experience or training for these men, and I question the likelihood of their seeing any more general surgical emergencies than are met in any average obstetric-gynecologic service.

Let us continue with the quotation. Amplifying his argument, this same authority said, "For example, suppose a gynecologist were to operate for a large fibromyoma of the uterus, and found a gall bladder full of stones." Insisting that such a man's operative ability must perforce be limited, he demanded to know what this operator would do. Would he remove the uterus, and meanwhile summon a surgeon to stand by to remove the gall bladder, or would he be so remiss toward the patient as to remove only the uterus and leave the gall bladder, because of his lack of general surgical ability? Apparently in the vehemence of his argument it did not occur to him to question the soundness of judgment of any surgeon who would subject his patient to a hysterectomy for fibroids, at the same time throwing in a cholecystectomy for good measure.

Another comment makes one ask what possible benefit in the way of general surgical training or experience can follow the subordination of gynecology as a division of general surgery in an institution from which the Dean writes as follows: "Female urology forms part of the work of our Department of Gynecology. Administratively the Department of Gynecology is considered to be a sub-department of Surgery. As a matter of fact it is largely autonomous. I doubt if the Professor of Surgery ever sets foot in the gynecologic operating suite."

Still another objection offered to the combination of obstetrics and gynecology is that "men trained in obstetrics and gynecology sooner or later drift into the practice of one or the other, seldom continuing with both. The majority, as they grow older, major in gynecology, dropping their obstetric work because of its arduous nature." I do not believe that this is true of the obstetrician-gynecologists trained by modern methods in the combined specialty. Even if it is so, they are better gynecologists and better teachers for having had their broad fundamental training and experience in these closely related branches.

A third argument was, "A man cannot operate on scheduled cases in the morning if he has been up all night with an obstetric case." In a recent paper, Stander dismissed this adequately by the comment that "all doctors specializing as obstetricians and gynecologists, have connections with hospitals, most of them first class, thanks to the efforts of the American College of Surgeons and the American Medical Association. Good hospitals with trained resident staffs are decreasing the necessity of all-night vigils with every patient in labor."

It was startling to have the Dean of another of these five schools write, "I think that we need more conservative obstetrics and think that this cannot be obtained by combining obstetrics and gynecology."

The Dean of the one school in which gynecology is divided between the surgical and the obstetric departments says, "Possibly the most important reason why gynecology is retained in part by the surgical service is the fact that it is felt that the general surgeon will continue to do the major portion of operative obstetrics for many years to come, if not indefinitely."

If there are other reasons against a combination of obstetrics and gynecology as a united specialty, they have not been given me. The relative worth of such arguments should be obvious.

EFFECTS OF UNIFICATION

Let us clearly understand what is meant by the unification of obstetrics and gynecology. It does not mean that one trained in the specialty of obstetrics and gynecology must practice both, but first that he will be better qualified in either branch because of his knowledge of the other. The time will soon come, in all probability, when all those who have been thus broadly trained will practice not merely one or the other, but both, because of the fascinatingly engrossing interrelationship of the two. It does not mean that any one can fairly contend that the general surgeon is unqualified or unfitted to do female pelvic surgery. The results of numerous brilliant surgeons, many of them Fellows of this Association now and in the past, refute such an implication or conclusion.

It does mean that there is a growing appreciation that the teaching of undergraduate medical students, and the training of graduate students, are best accomplished when obstetrics and gynecology are correlated by being departmentally united. Properly to teach the younger men who will succeed us, those giving the instruction should have a background of wide experience in both branches, and preferably should practice what they teach. Needless to say, both obstetrics and gynecology are non-elective subjects for undergraduate students, being "required" subjects in all American schools. The combination also means that patients requiring the solution of either gynecologic or obstetric problems will receive the greatest benefit if they are in the hands of men having this breadth of background.

Fundamentally and basically, therefore, the problem becomes one of training. Those who have had adequate education in the combined specialty should be similarly training the potential specialists. They can best do their teaching of the younger men, while these are serving as interns, assistant residents, and residents on combined hospital services. In institutions with medical school affiliations, these same trained men should be teaching obstetrics and gynecology and the elements of their interrelationship to the undergraduate.

Let us see how this applies in the three different groups of schools. In the hospitals of all of the 45 schools having combined chairs the resi-

dents, assistant residents, and interns are given a well-rounded and balanced service in the combined specialty.

In contrast to this, in the 23 having separate chairs, residents alternate or rotate through both services in only 4, and through obstetrics, gynecology, and surgery in only 4 more. There is a partial rotation in 1 other. At 13 of these institutions the residents serve either in gynecology or in obstetrics, but not in both, so that their training here is presumably deficient in one or the other.

The assistant residents fare about the same, as is shown in Table I, but internes are required more generally to serve in both departments.

In those in which the chair of gynecology is combined with that of surgery the residents rotate between surgery and gynecology in only 1, and between surgery, gynecology, and obstetrics in only 1 other. The assistant residents and interns have generally similar facilities, the importance of related obstetric training apparently being minimized.

Graduate training in obstetrics and gynecology presents two distinct aspects. There are many men who do not intend actually to specialize in this work but whose interest impels them to seek something more than the limited experience derived from an average rotating internship. Still others may have been in practice a few years, and wish to improve themselves in special work. One problem therefore concerns itself with the matter of providing graduate training for limited periods of time for these men. The other is that of providing training facilities for those planning to specialize in obstetrics and gynecology.

Many hospitals offer special internships for men who have completed a general rotating internship there or elsewhere. These services are usually for one year, and in many of these four men are appointed. This provides ideal training for a man who does not intend to specialize, but who plans to engage in general practice with special attention to obstetrics and gynecology. It is also a good foundation for those who propose to work up more slowly to specialization through the medium of dispensary and assistant staff attending positions in a department of obstetrics and gynecology of some general hospital.

If these same institutions could arrange assistant internships, externships, or voluntary assistantships for periods of three or four months, perhaps with a registration fee, they would probably be crowded with applicants. Such positions would be in great demand among general practitioners anxious to improve their knowledge and to bring themselves up to date from time to time. Unfortunately such opportunities are not generally available.

Assistant residencies, and residencies of one year each, as now provided, are usually obtained by promotion from the internships. For example, two of four interns are chosen to become the assistant residents, and one of these in turn is appointed to the residency for the ensuing year. At the majority of hospitals with such services, salaries as well as maintenance are paid to some of these men.

Certain hospitals in this country do not provide so complete a course of training, but absorb the assistant residents or even the interns who fail to obtain the promotion, or who wish to acquire other viewpoints by

going elsewhere. For example, many general and some special hospitals with assistant residencies and residencies prefer to have these men come to them from other clinics after their special internship of one year.

Thus, a variety of facilities for special training in obstetrics and gynecology are available in this country. Recently, a Committee on Graduate Education of the American Board of Obstetrics and Gynecology undertook to survey and list the institutions having services such as these. Its findings were published in the *American Journal of Obstetrics and Gynecology*,[5] in April, 1936, and should be consulted by those seeking such appointments.

To return to my original theme, I agree emphatically with Dr. Phaneuf that undergraduate teaching of obstetrics and gynecology should be from a combined chair. I reiterate the suggestion that graduate training is best given in a combined hospital service, and that the only compromise with this can be where provision is made for rotation of interns, resident assistants, and junior staff assistants between the two services. Even this is not as satisfactory as to give them their practical training under one head or director who is able from personal experience to correlate the teaching in the two branches. I subscribe wholeheartedly to the viewpoint of the American Board of Obstetrics and Gynecology that even those men who wish to practice or teach only one of these two branches are not adequately qualified to do so without a thorough training and experience in the fundamentals of both. I repeat that modern gynecology is not being well taught when its precepts come from a chair of general surgery, with the chair of obstetrics entirely alienated from the subject. The teaching of obstetrics and of gynecology suffers when their chairs are separated.

CHANGES IN TEACHING METHODS

If these concepts which I have presented are valid, how then may the situation be corrected in those institutions naturally resistant to revision of their longstanding traditions, yet inclined to conform with the current trends and to improve their methods of undergraduate as well as graduate teaching of our specialty?

I have no desire to appear in the role, alliteratively described by the late Barton Cooke Hirst, as that of a "nonteacher trying to teach teachers how to teach." It is quite possible, however, to acquire a viewpoint unaffected by local conditions or political expediencies, and to envision the matter entirely from the standpoint of results. Moreover, what is now being said about teaching institutions applies equally well to hospitals without teaching affiliations. The latter predominate numerically, and render an important service to the women of this country, incidentally providing training for many future specialists and practitioners in obstetrics and gynecology. I have ventured, therefore, to formulate certain ideas and to offer certain suggestions on this account, but not on this account alone.

In the position with which I have been honored for several years, namely that of Secretary of the American Board of Obstetrics and Gynecology, I have received an extraordinary number of communications on

TABLE I.—GYNECOLOGY AND OBSTETRICS IN THE
(FOUR-YEAR
TOTAL INQUIRIES
ANALYSIS OF

CHAIRS	TOTAL	PER CENT	DURATION OF COMBINATION	PRESENT ARRANGEMENT SATISFACTORY	ARRANGEMENT UNSATISFACTORY	CONTEMPLATING CHANGES
Gynecology and obstetrics combined	45	60.8	Within last 10 yr.: 16 Within last 20 yr.: 7 Longer than 20 yr.: 22	42 (No answer 2)	1	0
Gynecology and and obstetrics separate	23	31.0		15	8	Combination with obst. planned: 5 Combination with obst. under discussion: 1 Opinions divided: 1 No plans: 1
Gynecology and surgery combined	5	6.7	Within last 10 yr.: 1 Longer than 20 yr.: 2 No answer: 2	5	0	0
Gynecology combined partly with surgery, and partly with obstetrics	1	1.3		1		
Total	74			65	9	8

this very subject. The Deans of two medical schools, and the secretaries of a number of hospital staffs have addressed the Board to the effect that they have taken cognizance of the Board's demands that candidates for certification must have a specified minimum training in both obstetrics and gynecology. They have recognized that the logical way to provide this is by an integration of these departments. In some instances, this requirement of the Board may have had only a minor influence upon their decision, their altered viewpoint being initiated by the very force of the plan's own logic.

From these conferences a simple plan of procedure seems naturally to have evolved itself. It is not an official suggestion of the Board, because the Board is merely an examining body and has never undertaken

MEDICAL SCHOOLS OF THE UNITED STATES AND CANADA

"GRADE A" SCHOOLS)

75—REPLIES 74

TEACHING PLANS

DEPARTMENT HEADS			HOUSE-STAFF TRAINING IN OBSTETRICS-GYNECOLOGY								
FULL TIME	PART TIME	CLINICAL	SERVICE	OBST.-GYN. COMBINED OR HAVING INTER-ROTATION	OBST.-GYN. SEPARATED: NO INTER-ROTATION	OBST.-GYN. SEPARATED: PARTIAL INTER-ROTATION	OBST.-GYN. AND SURGERY INTER-ROTATION	GYN. SURGERY INTER-ROTATION WITHOUT OBST.	NO ANSWER	UNDERGRADUATE TEACHING OBSTETRICS-GYNECOLOGY REQUIRED SUBJECTS	
10	20	14	Resident	45						45	
Obst. part time & gyn. "clinical" 1			Asst. resident	45							
			Interne	45							
1	8	7	Resident	4	13	1		4	1	23	
Obst. part time, gyn. clinical: 5 Obst. full time, gyn. part time: 1 Obst. full time, gyn. clinical: 1			Asst. resident	3	12	1		3	4		
			Interne	11	3			7	2		
0	2	3	Resident		2		1	1	1	5	
			Asst. resident				2	3			
			Interne		1		1	3			
1 (Modified)			Resident		1					1	
			Asst. resident		1						
			Interne				1				
12	30	24	Resident	49	16	1	1	5	2	74	
			Asst. resident	48	13	1	2	6	4		
Mixed 8			Interne	56	4		1	10	2		

to interfere with or direct the policies of any group or institution. The Board does no more than establish certain minimum standards of education and training as a basis for admission to its examinations.

The Dean of one school of medicine wrote some time ago that the trustees wished to reorganize their departments of obstetrics and gynecology, combining the chairs into one, and asked if we had any suggestions to make as to how the new department should be organized and conducted. He said in effect that he dreaded the repercussions, and the disappointments of some who would be adversely affected by the change, but that they were all convinced of the wisdom of the move. His letter came at about the same time that one of a similar nature was received from another Dean of a school in which one chair had been vacated by

the death of the incumbent. During the same period others were received which related to the reorganization and combination of departments in three hospitals without teaching or medical school affiliations. After considerable correspondence, and even some personal conferences, certain facts developed. At the outset, it was clear that in all such institutions, a general upheaval is undesirable. Those men who have supported them faithfully for years should not be slighted, but obviously should be retained and absorbed wherever possible in any such reorganization.

The principal difficulty seemed to be that of the choice of a director for any new department of obstetrics and gynecology. In one instance the importation of a man from elsewhere solved their problem; in another, they appointed the senior man who limited his work almost entirely to gynecology, although he had had excellent training in obstetrics; in the institution in which a vacancy was created by death, the occupant of the other chair was given the new combined post; in still another, the younger of the two men was selected solely because he had had a broader training and was better equipped.

Under these heads, holding the newly combined chair or staff position, it was suggested that a professorship, or senior staff position, in obstetrics and similarly one in gynecology be created, subordinate to the head of the combined department, with respective groups of associates and assistants being given lesser positions so that the whole formed a strong pyramid with a broad base. No dismissals were necessary, no demotions were required, and no restrictions of duties or privileges needed to be imposed. Indeed, the activities of all department members, previously restricted by the limits of their department, were immediately broadened in scope and interest, according to an individual's ability. A new administrative head of the combined department having been appointed, his greatest responsibility became that of coordinating the work of the two groups as rapidly as possible. Such a reorganization must necessarily be developed gradually. In certain instances it involved additional graduate training for some of the department members themselves. A gradual fusion with the least possible, but occasionally necessary, elimination or restraint of those unable to adapt themselves was infinitely wiser than an abrupt and sweeping change in any of these institutions.

The most important reform of all was that whereby the resident house officers and students were compelled to weave their activities into the work of the two groups without any imaginary or arbitrary dividing line, so that instruction and training in gynecology and obstetrics were integrated by clinical precept and management of cases.

TYPES OF PROFESSORSHIPS

In the questionnaire, due notice was taken of the material or financial side of this question as this is of considerable importance to all schools which must function usually with less than adequate endowments. Reference to the table shows that the part-time professorship plan predominates in North American schools.

Full-time professorships are those under which the incumbent is paid a salary and gives his entire time to the position he holds; part-time professors receive a lesser salary as reimbursement for their school activities but are allowed the privilege of a limited amount of consultation and other "private" work. The professorship designated here as "clinical" is that under which the school pays no salary, and the incumbent's entire livelihood comes from his clinical or "private" practice.

The first of these is a fairly recent innovation about which certain objections have been raised. It has been said that the full-time professor, by being cloistered, is forced out of touch and out of sympathy with the general medical profession. Local jealousies seem prone to develop and the school's hospital and special services suffer not only from nonsupport but often from active opposition from the local profession. This is especially true in those places where private patients are admitted to the care of a full-time specialist, the institution taking the patient's medical fee. The profession objects that such an institution is actively competing in the practice of medicine with the physicians of that community.

Capable men who take these positions must make considerable financial sacrifices because their earning powers in ordinary private practice are usually considerably more than the salaries which their institutions can afford to pay them. Consequently, such men are relatively few in number, not easily found, and their institutions impose a constant hardship on them at the same time that they expect and receive the intense loyalty of these men.

The third or "clinical" type of professorship is one which is often dictated by necessity. An outstanding man in a school's community, supporting himself entirely by his clinical practice, may have been chosen outright or may have worked up to the professorship through promotions. His compensation for his school work is the prestige of the position, and the consultation work which may come later from the students he has taught and trained. His personal interests usually come first, because he is no more than human, and his school work is often secondary to the demands of his practice. In the selection of such men the school is ordinarily limited in choice to practitioners in the school's immediate vicinity.

The part-time professorship seems to be an ideal compromise between these other two plans. This survey demonstrates that it is the most widely favored plan at the present time. From the standpoint of the school it is more economical than the full-time professorship. It is less restrictive and more broadening in opportunities for the individual, and generally more inviting to any capable man than either of the others. Under this plan, men may be attracted to come to a school from elsewhere if that is desired, or local men find it possible to discontinue the routine and relatively unimportant parts of their private work in order to give more time to the school.

Incidentally it may be remarked that under either the full-time or part-time plan, the unification of the departments of obstetrics and

gynecology is, obviously, an economical move so far as salaries and other administrative expenses are concerned.

GENERAL

This transition which has been discussed is still going on. In those places where it is complete, the general surgeon no longer fears or finds that the gynecologist wishes to invade his domain, obviously with less skill than that possessed by the general surgeon. In fact, indiscreet excursions into general surgery by the gynecologist constitute another valid reason against the policy of including gynecology in the department of general surgery. Obstetrics and gynecology is a field of sufficient breadth to test the skill, engross the entire interest, and require the full attention of any one man. Working in such a broad specialty he will have no inclination or time, even in the unlikely event that he possesses the ability, to invade the field of general surgery.

Furthermore, in the course of due time, it should be found that the obstetrician-gynecologist will have less and less occasion to object that the general surgeon in his institution continues to undertake female pelvic surgery. Comparison of results between the two departments should take care of this situation, and if they fail to prove his advantage something is wrong with the gynecologist.

Criticism, to justify itself, should be constructive. What then shall be the constructive thought which should accompany the criticism in this address?

It is obvious that specialization in any field of medicine can be improved by higher educational standards and better training facilities, to the end that our sick populace will benefit when the help of a specialist is needed, whatever the nature of his affiliations. For the protection of the public, if there are to be specialists in the several branches of medicine, let us make certain that they are well trained and not merely self-styled ones. What this country needs is not more but better specialists. Adequate training through the medium of hospital residencies or of staff assistantships for prolonged periods of time is the only reasonable solution to this.

Our particular problem in this march of progress is specialization in obstetrics and gynecology. I am convinced that our answer is to be found in the unification of obstetrics and gynecology into one specialty for the purposes of teaching of students, clinical training of one's assistants, and actual practice for oneself, all to the immediate advantage of the patients for whom we are caring.

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STUDIES ON THE ENDOMETRIUM IN ASSOCIATION WITH THE NORMAL MENSTRUAL CYCLE, WITH OVARIAN DYSFUNCTIONS AND CANCER OF THE UTERUS*†

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A WORKABLE classification of the endometrial findings in the normal menstrual cycle has been outlined in previous papers.[1-3] The classification was based on a study of 241 endometrial specimens removed either at dilatation and curettage or by means of the Randall uterine biopsy instrument.

CLASSIFICATION OF OVARIAN DYSFUNCTION

A fairly simple clinical classification of the various types of ovarian dysfunctions also has been adopted. In general, they are divided into two large groups: the "primary ovarian dysfunctions" and the "secondary ovarian dysfunctions." In the former group failure is primary in the ovary itself. In this group, one is confronted not only with the problem of menstrual irregularity, and often sterility, but also with a train of symptoms associated with true ovarian failure. There is no evidence in this group of pituitary disturbances such as abnormal fat metabolism, abnormal water metabolism or lowered basal metabolic rate.

The second large group includes the primary pituitary and thyroid failures in which ovarian failure is, of course, a secondary phenomenon. In this group evidence of disturbances of fat metabolism as well as of water metabolism and lowered basal metabolic rate often are found. This, roughly of course, constitutes the clinical classification.

From the histologic standpoint the evidence of ovarian dysfunction, however, is the same in both groups since the endometrial pattern changes with ovarian function regardless of whether the cause of its abnormal function comes from within or from without the ovary. It becomes apparent, therefore, that one cannot classify these dysfunctions on the basis of the histology of the endometrium only but histologic examination does form a part of the armamentarium in arriving at a rational diagnosis. Biopsy of the endometrium, with study of its histologic characteristics, is of greatest value in recognizing a subdivision of these ovarian dysfunctions into the groups of partial or complete ovarian failure, regardless of whether the failure is primary or secondary. Since the regenerative phenomenon seen in the endometrium

*First award of the Foundation prize essay of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons. Read at the Fifty-First Annual Meeting of this society, White Sulphur Springs, W. Va., September 22 to 24, 1938.

†Because of consideration of space this essay is abridged for publication here. The complete paper will appear in the Transactions of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons for 1938.

depends on the ovarian hormones for its stimulus, any degree of failure of this stimulus, or stimuli, can be recognized. The proliferative phases of the endometrial cycle, as has been seen, are dependent on the follicular hormone, and the differentiative phases depend on the normal activity of the luteal hormone. If either of the hormones is absent or deficient, then the regenerative phases likewise will be absent or deficient. Further, the prolonged activity of one or the other hormone will result in prolongation of the phase controlled by this hormone.

On the basis of this histologic and physiologic explanation I have proposed the term "persistent phases of the cycle" which at once denotes the deficiency in ovarian function which is manifested by the endometrial change. The interpretations have been consistent to the degree that often it is possible to predict the type of clinical syndrome associated with a given histologic pattern.

As examples of the persistent phases mentioned above, which are associated with ovarian dysfunction, a few of the representative tissues are here presented.

Persistent Early Proliferative Phase.—The word "persistent" used in this classification denotes the histologic state of the endometrium and at the same time postulates abnormal function of the ovary. For example, an ovary that is deficient in production of luteal hormone and that is to some degree deficient in follicular production will express these changes by a lack of development (or regeneration) of the endometrium, and the endometrium, therefore, will remain in a state of persistent proliferation. Such an endometrium is not hypertrophied or hyperplastic in any sense—in fact, often such an endometrium will appear microscopically the same as the endometrium usually seen in the first seven days of the normal cycle. It is obvious, therefore, that a pathologic diagnosis need not be made but rather a report of the degree of ovarian failure can be given. In addition to histologic accuracy, such a report is of more diagnostic value to the clinician than is a pathologic diagnosis. The specimen shown here (Fig. 1) represents an endometrium removed on the twentieth day of an abnormal cycle. This specimen, if it had been taken on the twentieth day from a patient whose cycle was normal, should give evidence of differentiation, which is a normal corpus luteum effect. However, histologic study discloses that the endometrium is arrested in the proliferative phase. The patient was a bleeder who previously had been given theelin; incidentally this produced more, rather than less, bleeding. It becomes clear that this patient did not lack theelin, which is the proliferator of the endometrium, but rather the deficiency is one of stimulation by corpus luteum. The treatment indicated, therefore, is one which is designated to bring about stimulation of the corpus luteum. This same type of endometrium may also be seen *occasionally in cases of amenorrhea; nevertheless,* the basic disturbance in the ovary is the same. The problem of the exact cause of bleeding obviously still baffles students of this subject.

Persistent Late Proliferative Phase.—The principles outlined in the preceding paragraph apply in examination of specimens in this phase. Again the endometrium reflects the state of ovarian function and the difference herein is one of degree rather than of kind. A persistent late proliferative phase found on examination of a specimen of endometrium removed in the last part of a regular, or of an irregular, cycle denotes merely that a full proliferative or follicular effect has been exerted on the regenerating endometrium. The only ovarian deficiency evident in this phase, therefore, is in production of the luteal hormone. Again, the change is not hyperplasia but arrest of the regenerative phenomenon. Patients whose tissues can be classified in this group, interestingly enough include the largest number of bleeders, and, therefore, constitute clinically one of the most important groups of patients. The treatment likewise is not by administration of theelin but of a luteinizing hormone. The endometrium usually will have characteristics almost identical with

those of a normal late proliferative phase of a normal cycle. The glands are somewhat dilated but they are straight, tubular glands; approximately six such glands are found per low power field. The gross thickness of the endometrium usually is not more than 2+ mm. Fig. 2 represents a state of persistent late proliferation in an endometrium removed on the twenty-third day of the cycle. This patient complained of hypomenorrhea but her cycle was fairly regular. Her primary complaint was sterility although patients of this group usually complain of menorrhagia. This patient's urinary estrin content was normal but pregnandiol was completely absent from a twenty-four-hour specimen of her urine. This indicates complete absence of the luteinizing hormone.

Persistent Early Differentiative Phase.—The types of abnormal ovarian function associated with tissue classified in this group are interesting. A state of persistent early differentiation denotes, as would be expected, partial failure of corpus luteum and again the endometrium appears like that seen in the third week of the normal cycle, in which there has been a partial but not a complete luteal effect on the

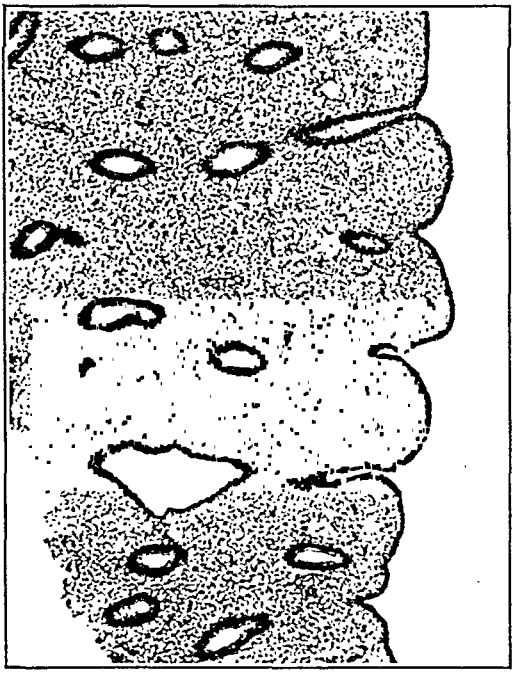


Fig. 1.



Fig. 2.

Fig. 1.—Persistent early proliferative phase of menstrual cycle. Glands identical with those seen in the first phase of the normal cycle; they are small, straight, tubular glands lined with low epithelium. This endometrium does not differ from normal endometrium in any respect except that it was removed in the last part of a cycle and it contains an occasional cyst. No actual increase in the total number of glandular elements (although previously called hypertrophied or hyperplastic endometrium). Average thickness of endometrium, 1 mm. Hematoxylin and eosin (×50).

Fig. 2.—Persistent late proliferative phase of the menstrual cycle. Average thickness of endometrium approximately 2 mm. Glands nearly identical with those found in same phase of cycle in a normal endometrium in the late proliferative phase. Average number of longitudinal glands per low power field is six. Hematoxylin and eosin (×50).

endometrium. Bleeding is less among the patients corresponding with endometrium of this group than among those mentioned in the preceding paragraph. Differentiation may, therefore, to some degree prevent the bleeding. One of the common findings in this group is sterility and there are a few cases of hypomenorrhea. The histologic characteristics are not greatly different from those of the normal early differentiative phase. The number of glands is essentially the same. In this group the glands are more convoluted and the proliferative epithelium changes, under partial corpus luteum effect, to a more columnar differentiative epithelium. The gross thickness of the endometrium is approximately 3 mm. The specimen illustrated

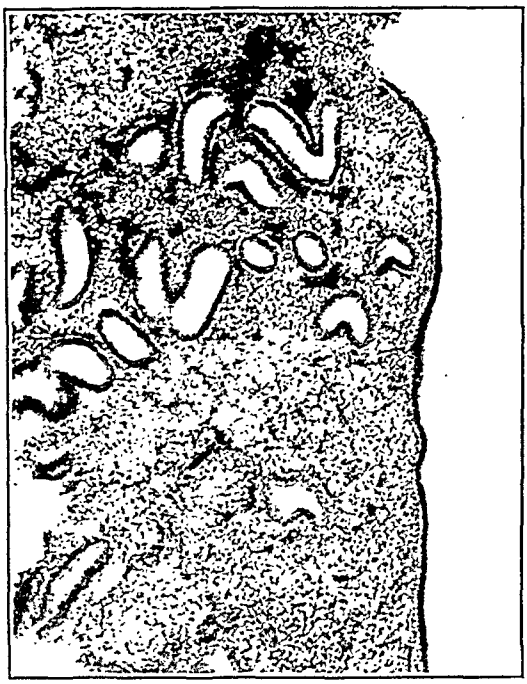


Fig. 3.

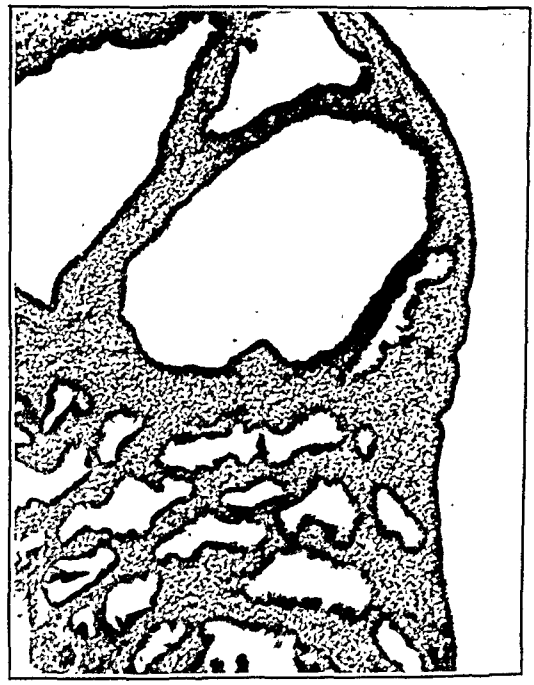


Fig. 4.

Fig. 3.—Persistent early differentiative phase of menstrual cycle. The longitudinal glands are characteristic of the early differentiative phase. The glands are lined by columnar epithelium and have convolutions which are normal for the early differentiative phase, that is, the fourteenth to twenty-first day of the cycle. The average number of longitudinal glands per low power field is six to seven. Endometrium does not differ greatly from the normal yet was taken at the time of the cycle when differentiation should be complete. Some effect of the corpus luteum hormone is evident in the endometrium. However, absence of complete differentiation indicates a partial failure. Hematoxylin and eosin (×50).

Fig. 4.—Persistent late differentiative phase of the menstrual cycle in a cystic endometrium. Complete differentiation is evident. There are six to seven longitudinal glands to the low power field but differentiation is complete. The abnormal feature is the presence of cystic areas existing in an endometrium which histologically gives evidence of the nearly complete effect of the hormone of the corpus luteum. Hematoxylin and eosin (×50).



Fig. 5.—True atrophic endometrium result of dilatation and curettage or biopsy. Note small islands of epithelial cells with loose stroma. Hematoxylin and eosin (×50).

(Fig. 3) was removed from a patient who complained of sterility and who, following stimulation by corpus luteum, became pregnant.

Persistent Late Differentiative Phase.—When the degree of ovarian failure is small, that is, when there is nearly a complete luteinizing effect on the endometrium, the histology of the endometrium is also only slightly altered. Differentiation is complete, or nearly so, but clinically there may be some slight abnormality in the menstrual cycle. However, most of the patients menstruate regularly and complain of either sterility or of some symptom suggestive of ovarian failure. Such an endometrium as that under consideration usually will contain six to seven longitudinal glands per low power field. In longitudinal section these glands appear as a sectioned seashell. The glands are lined by columnar, differentiated epithelium. Cases of this sort are favorable to treat because only slight stimulation often will correct the dysfunction. Cystic changes often are seen in this type of endometrium and constitute a very definite abnormal finding (Fig. 4).

Atrophic Endometrium.—The term "atrophic endometrium," like "hypertrophic endometrium," has been rather loosely used. It has been applied to menopausal as well as to postmenopausal endometrium; however, observations made in this study would indicate that the term "true atrophic endometrium" would be more applicable to that type of case in which complete and rather sudden ovarian failure has occurred. Following sudden failure (either spontaneous or artificial failure, that is, surgical removal of the ovarian tissue), there occurs a lack of both the follicular and corpus luteum stimulus to endometrial regeneration, and hence, true atrophy occurs. The gradual failure of the ovaries incident to the climacteric is usually associated with cystic formation as stated above. However, as stated, sudden withdrawal or failure of ovarian tissue is accompanied by true atrophy. The remaining endometrium consists of a single layer of epithelium overlying a loose stroma. This is typical of true atrophic endometrium, biopsy of which or even vigorous curettage will result in securing only small amounts of endometrial tissue. However, a diagnosis can be made on the presence of small islands of epithelial cells lying usually in the loose stroma described above. Fig. 5 illustrates true atrophic endometrium removed from a patient twenty-nine years of age who presented amenorrhea with sudden onset twelve months before admission.

THE ENDOMETRIUM ASSOCIATED WITH CANCER

The foregoing studies have had to do primarily with endometrial histology in association with the normal cycle as well as with the endometrial findings in association with ovarian dysfunction. I am of the opinion that the classification outlined is more useful than previous classifications in the field of surgical pathology of endometrium obtained by the usual methods, namely by biopsy and curettage. In fact, this classification is now used at The Mayo Clinic in the diagnosis of normal and abnormal endometrial tissues.

Subsequent to the studies to which reference has just been made, the characteristics of endometrium associated with malignancy of the body of the uterus have been investigated in 50 cases. For this study sections were made of endometrium from different parts of uterine fundi removed for carcinoma; some of these sections were taken in an endeavor to show endometrium in transition from the nonmalignant to the malignant portion. In addition to this, the ovaries were carefully sectioned in all cases in which the endometrium was studied. Carcinoma of the uterine cervix was entirely excluded from the study since the cervix is, of course, little if any affected by the activity of the ovary except under certain physiologic conditions.

The clinical data were, of course, collected in each case but are not pertinent to the present investigation except with relation to the age of onset of the menopause.

The most confusing factor in studies of this nature to date has been the various attempts on the part of many observers to associate so-called endometrial hyperplasia with the existence or development of carcinoma of the uterus. Such attempts are more confusing than clarifying. One has only to review the reports on this type of hyperplasia to learn that it has been blamed for amenorrhea, menorrhagia, sterility, fibromyoma, abortion, and now, carcinoma. In fact, there is hardly a gynecologic syndrome which has not been associated in some way with this "waste-basket" diagnosis of endometrial hyperplastic change. The studies reported herein present, however, I believe, ample evidence that such a diagnosis is not justified without qualification.

The possible rôle of hyperplasia in association with carcinoma of the endometrium has been suggested by Meyer,[4, 5] Schröder,[6] and Taylor,[7] and, recently, by Novak and Yui.[8] The report of the last named authors is based on the finding of endometrial hyperplasia in 25 per cent of cases of carcinoma of the uterus. Concerning the remaining 75 per cent, no special type of endometrium is described other than atrophic endometrium. Excellent work by Payne[9] has thrown much doubt on the possible causal relationship of hyperplasia to malignancy. He found the incidence of hyperplasia with superimposed or associated carcinoma to be only 2.4 per cent which would indicate a rather rare relationship if such ever occurred. Likewise, Burch stated, "I have never seen the two conditions associated together in the same patient, nor have I ever seen hyperplasia as a forerunner of cancer." With this statement I thoroughly agree. The mere fact that the statements are so widely divergent is ample evidence that "hyperplasia" is a most useless and confusing term and represents a microscopic diagnosis which is of little value. Certainly, the process can hardly be related to malignancy in the light of the reports available to date.

In study of microscopic sections of endometrium taken from portions not involved in malignancy, and of sections taken from portions adjoining the malignant tissue, I have been able to classify the endometrium in terms corresponding to those used to describe the tissue characteristic of the various phases of the cycle; these terms are explained earlier in this report. Casual examination of the illustrations will at once indicate that in practically every specimen the endometrium was similar to that seen in the early or late proliferative phases of the cycle. This type of endometrium always results from the action of estrin (follicular hormone) on the endometrium.

Fig. 6 represents the endometrium of a patient, aged 52 years, who had an adenocarcinoma, Grade 1, of the endometrium. The endometrium is nearly identical with that of a menopausal patient (Fig. 7). The glands are of the small, straight, tubular type and are lined with low cuboidal epithelium of the proliferative type. The ovaries of this patient contained many cysts, lined by granulosa cells, and histologically identical with the ordinary follicular cysts. There were no corpora lutea. The gross thickness of this endometrium was approximately 0.5 mm. and obviously was not hyperplastic.

Fig. 8 likewise represents a specimen of endometrium removed from a patient 61 years of age, who had not menstruated for six years until one month before operation for carcinoma of the uterus. This endometrium was not atrophic nor was it

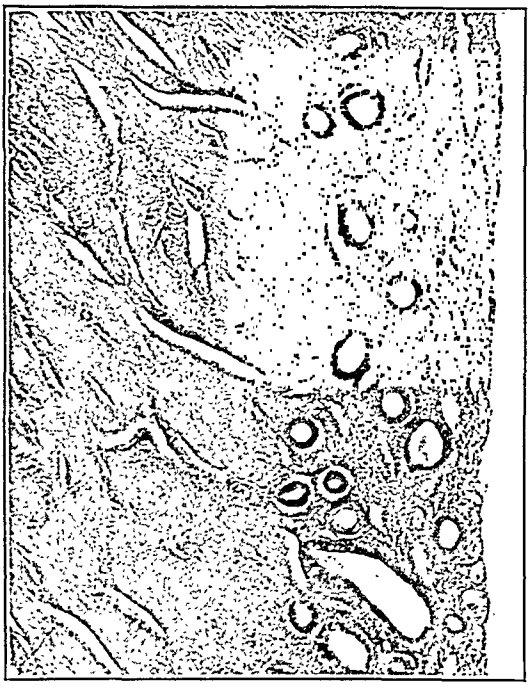


Fig. 6.

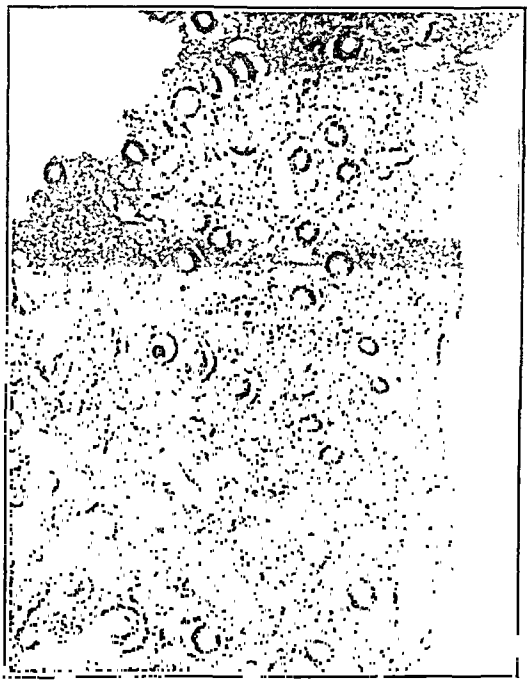


Fig. 7.

Fig. 6.—Persistent early proliferative type of endometrium. Photomicrograph of a specimen removed near an area of malignancy of the fundus. Hematoxylin and eosin (×50).

Fig. 7.—Typical persistent early proliferative phase. Specimen removed from a patient who did not have malignancy but who was in her menopause. Histologically almost identical with Fig. 6. Hematoxylin and eosin (×50).



Fig. 8.



Fig. 9.

Fig. 8.—Proliferative type of endometrium with cystic change. Photomicrograph of a specimen of endometrium removed from the fundus of a uterus in which there was a carcinoma. This is a typical early proliferative type of endometrium with cystic change. Hematoxylin and eosin (×50).

Fig. 9.—Early proliferative type of endometrium with cystic change associated with carcinoma of the endometrium. Photomicrograph of a specimen from the same patient as represented in Fig. 8 except that this specimen was removed adjoining the area of malignancy. Note transition from early proliferative type with cyst on the left to an area of malignancy shown on the right. Hematoxylin and eosin (×50).

hyperplastic. It was of typical early proliferative type and cystic change had taken place; this denotes absence of corpus luteum yet a positive effect of estrin. The right ovary in this case contained an adenocarcinoma, Grade 2. The left ovary contained a cyst, 2 cm. in diameter, and several other microscopic cysts. Fig. 9 represents the same endometrium adjacent to the region of malignancy and is of the same type; namely, proliferative in a cystic endometrium.

Fig. 10 represents the endometrium of a patient aged 56 years, who one year after cessation of her menses began to have menorrhagia, which was found to be owing to a carcinoma of the fundus, Grade 1. This specimen of endometrium was removed from a portion in which there was no cancer. This was a typical proliferative type of endometrium with cystic portions which histologically were identical with those previously shown to occur in association with the ovarian failure that is attributable to lack of any luteinizing effect. However, there was definite evidence

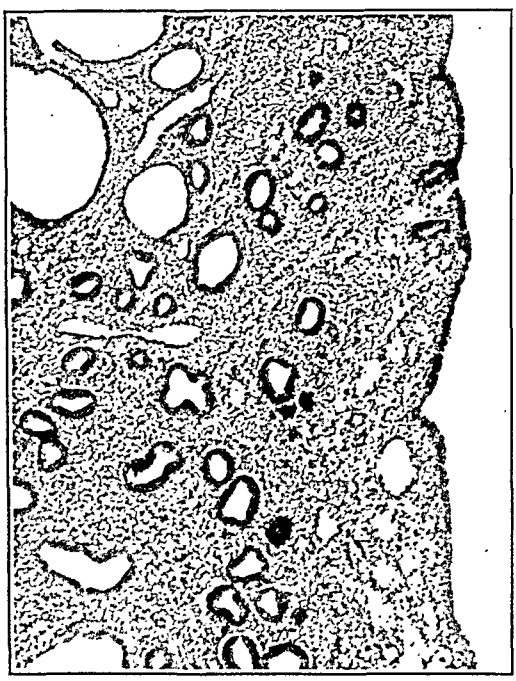


Fig. 10.



Fig. 11.

Fig. 10.—Proliferative type of endometrium with cystic change. Specimen removed from the endometrium not adjoining the malignant area. This is a characteristic picture of theelin effect and an absence of corpus luteum. Hematoxylin and eosin (×50).

Fig. 11.—Proliferative type of endometrium directly adjoining Grade 1 adenocarcinoma. The left side of this photomicrograph shows a typical adenocarcinoma, Grade 1, while the right side shows a typical proliferative type of endometrium. Hematoxylin and eosin (×50).

of persistent follicular, or theelin, activity and this endometrium was denoted as of persistent proliferative type, with cystic change. Fig. 11 represents the endometrium adjacent to a malignant portion. In the upper right portion of the figure there are normal, or nonmalignant, glands of proliferative type adjoining the area of adenocarcinoma, Grade 1, shown on the left. The ovaries of this patient contained multiple cystic portions, many of which histologically resembled the follicular cyst.

Fig. 12 illustrates the endometrium adjoining the area of adenocarcinoma, Grade 2, of the uterine fundus, removed from a patient aged 54 years, who had experienced the menopause four years before onset of the symptoms which were proved to be attributable to the carcinoma. Microscopically, this illustration shows, on the left, a rather typical adenocarcinoma, Grade 2, and immediately adjoining it an endometrium which is of the persistent early proliferative type and which has undergone cystic change. Both ovaries of this patient contained multiple cystic portions,



Fig. 12.

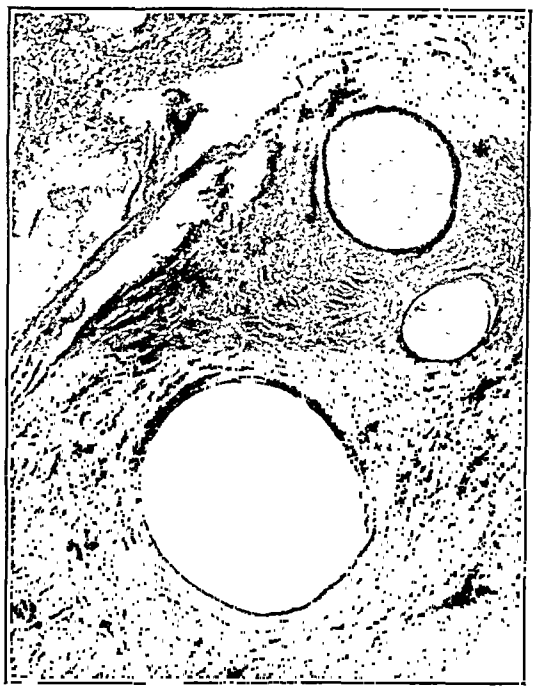


Fig. 13.

Fig. 12.—Proliferative type of endometrium with cystic change immediately adjoining an area of adenocarcinoma, Grade 2, of the endometrium. The left portion of this photomicrograph represents a typical carcinoma immediately adjoining the type of endometrium described as proliferative. Note absence of any lutein effect. Hematoxylin and eosin (×50.)

Fig. 13.—The ovary associated with malignancy of the fundus. This is a photomicrograph of a specimen of one of the ovaries in the same case which is shown in Fig. 12. Note the multiple cystic areas, some of which are filled with homogenous material. Hematoxylin and eosin (×50).



Fig. 14.



Fig. 15.

Fig. 14.—One of the cysts shown in Fig. 13 viewed under high power objective. Note the typical granulosa cell lining of the cysts shown here. Hematoxylin and eosin (×200).

Fig. 15.—Early proliferative type of endometrium associated with malignancy. Note the typical early proliferative type of endometrium in the left portion of this figure and the immediate transition to malignancy. Hematoxylin and eosin (×50).

some of which are represented in Fig. 13. One of these cystic portions, photographed at a higher magnification, is represented in Fig. 14. This cyst contains homogeneous material. The wall of the cyst was lined by typical granulosa cells. No corpora lutea were demonstrable.



Fig. 16.

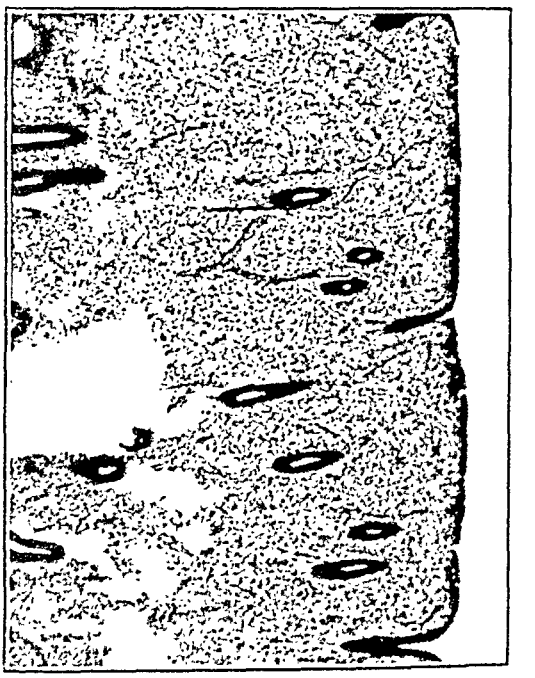


Fig. 17.

Fig. 16.—Early proliferative type of endometrium in transition to malignant area. The lower portion of this figure is a benign, typical proliferative type of endometrium and immediately above it is shown an area of adenocarcinoma, Grade 2. There is no evidence of hyperplasia in any of the figures shown. Hematoxylin and eosin (×50).

Fig. 17.—Early proliferative type of endometrium in association with malignancy. The patient from whom this specimen was removed had not reached her menopause but had a malignant growth in the endometrium. This specimen is almost identical with that shown in Fig. 1, namely, early proliferative type of endometrium due to the action of estrin. Hematoxylin and eosin (×50).

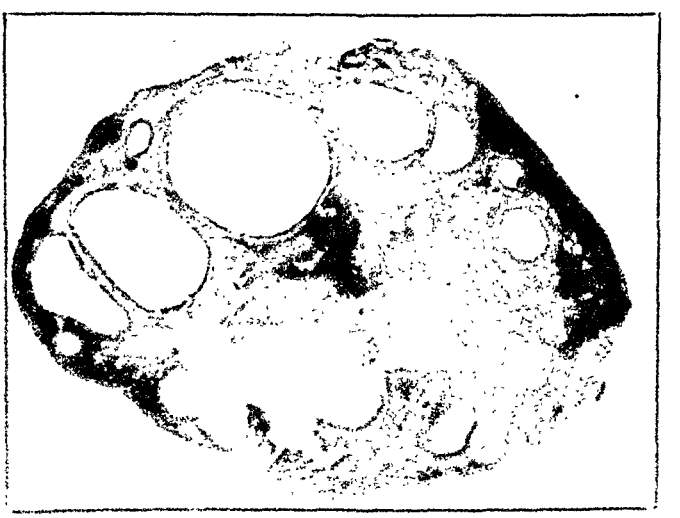


Fig. [illegible] cystic degeneration of one of the ovaries associated with carcinoma of the fundus. Note the multiple cysts, some of which are typical of follicular cysts [illegible] absence of any corpus luteum. Hematoxylin and eosin (×2).

Fig. 15, likewise, is of a specimen removed from a patient aged 53 years whose menopause was completed approximately one year before the onset of spotting and bleeding which was proved to be owing to adenocarcinoma, Grade 2. This also was a typical early proliferative type of endometrium, containing one small cyst adjoining a definite area of malignancy. One of the ovaries in this case contained a single cyst.

Fig. 16 represents another specimen which shows a definitely early proliferative type of endometrium immediately adjoining the area of an adenocarcinoma, Grade 2. This specimen was removed from a patient who had had her menopause six years prior to the onset of a pseudocycle, with bleeding and menstrual spotting. This specimen shows no definite cyst but is a typical proliferative type of endometrium. One of the ovaries of this patient contained a carcinoma.

The specimens referred to in the previous paragraphs were removed from patients who had had what could be considered a menopause, followed by the onset of bleeding at intervals after the menopause. Fig. 17 represents the endometrium of an individual aged forty-six years, who was not past her menopause but whose symptoms were essentially those of diffuse menorrhagia, with an interval of three to five weeks for three years, but whose cycle had never ceased. This endometrium, like that of patients past the menopause, was typical of an early or late proliferative type of endometrium and histologically was nearly identical with that represented in Figs. 1 and 2 of this paper, which was obtained from an individual whose endometrium was in the proliferative phase of the normal cycle. The endometrium represented in Fig. 16, therefore, denoted not hyperplasia but merely presence of activity of theelin and absence of any luteinizing or differentiating effect. There were bilateral cystic ovaries also in this case.

Fig. 18 represents the typical, rather characteristic type of ovary found in most of these cases in which the endometrium was the site of malignancy. The endometrium of the noncancer-bearing portion of this patient's uterus was of the typically early proliferative type, with cystic change. In Fig. 18 are represented multiple cysts lined with granulosa cells.

The foregoing are rather typical specimens of the entire series studied, in all of which the type of endometrium was essentially the same. The results of the type of endometria associated with malignancy and the ovarian findings in the 50 cases are shown in Table I. The time between cessation of menses and onset of symptoms suggesting malignancy did not alter the type of endometrium. Of especial interest is the fact that in all except 2 cases the endometrium was of the proliferative type even though 13 (26 per cent) had not reached the menopause, and were still on definite cycle. There was complete absence of differentiation and no corpora lutea were present in the ovaries. In addition to the cystic changes, the ovaries of 10 per cent of these patients contained

TABLE I.—SUMMARY OF STUDY OF ENDOMETRIUM AND OVARIES ASSOCIATED WITH MALIGNANCY OF THE UTERINE FUNDUS; 50 CASES*

TYPE OF ENDOMETRIUM	CASES	PER CENT	OVARIES	CASES	PER CENT
Proliferative without cystic change	14	28	Cystic without malignancy	12	24
			Cystic with malignancy	1	2
			Not cystic	1	2
Proliferative with cystic change	34	68	Cystic without malignancy	23	46
			Cystic with malignancy	7	14
			Not cystic	4	8
Differentiative	2	4	Cystic without malignancy	2	4
			Cystic with malignancy	0	0
			Not cystic	0	0

*In 13 cases (26 per cent) the patients had not reached menopause.

cystic or solid adenocarcinomas which were not metastatic except in one case. This emphasizes the importance of routine bilateral oophorectomy (Table I).

It is difficult to establish the fact that cysts such as occurred in the ovaries of the patients studied are productive of estrin, since there may be sources of estrin other than those known at present. It is true, however, that Fluhmann[10] has been able to demonstrate the presence of estrin in the blood of patients in the postclimacteric period when, as is known, cancer occurs; that is, approximately 75 per cent of cancers of the body of the uterus occur when patients have passed the menopause. An effort has been made in this study to determine the presence of output of estrin by individuals who have cancer of the uterus and the determinations herein reported were made on the urine. Recently I have been able to collect twenty-four-hour specimens of urine in 10 cases in which carcinoma of the uterus was proved to be present, and in 8 of these (80 per cent) positive values for estrin, in amounts of 5 rat units or more, were demonstrable. These patients were in the postclimacteric state and the positive values are, therefore, not owing to the regular menstrual cycle. This observation is particularly interesting in view of the fact that histologically evidence is available in the endometrium, as well as in the ovary, of the presence of this hormone, a fact which is demonstrated by this series of cases.

Analysis of Data on Carcinomatous Endometrium.—Of the 50 cases of endometrial carcinoma of the fundus studied, in 48 (96 per cent) the endometrium was of the proliferative type. In 71 per cent of these 48 cases, the endometrium was of early proliferative type and was associated with cystic change. It has been definitely shown, in the foregoing studies, that this type of endometrium is owing to continued follicular (estrin) activity and failure of the corpus luteum. This type of endometrium is not the so-called hyperplastic endometrium and the diagnosis "hyperplastic endometrium" has led to much confusion in attempts to correlate the endometrium of noncancer-bearing portions with that of cancer-bearing portions. In only 4 per cent (two cases) of this series of 50 cases was a diagnosis of differentiative type of endometrium allowable. The ovaries of both of the patients concerned contained normal corpus luteum; this constitutes still further evidence of the differentiating effect of corpus luteum.

Microscopic and macroscopic cysts of the ovary, lined by granulosa cells typical of follicular cysts, were demonstrable in 90 per cent of the cases in which carcinoma arose in the endometrium. That these cystic portions are possible sources of folliculin is easily possible from a histologic standpoint. Corpora lutea were usually absent. Twenty-six per cent of the patients were in the menstruating age, a fact which would indicate that the absence of corpora lutea in the ovaries was not owing to menopausal or postmenopausal factors but rather it would seem that the absence of corpora lutea is a true accompaniment of the lesion in the endometrium.

It is of interest that castration produces sudden cessation of action of both ovarian hormones on the endometrium and that the histologic result in the endometrium is production of a truly atrophic endometrium. However, gradual ovarian failure, such as occurs in the menopausal state or in association with ovarian dysfunction of younger women, usually is owing to the failure, first, of the corpus luteum; the result, for a time, is a persistent follicular (or estrin) effect. This, in turn, results in the production of an entirely different type of endometrium, namely, a persistent proliferative type, usually with cysts

The persistent proliferative type of endometrium has been shown by this work to be definitely indicative of the unopposed action of the follicular hormone, and this was the type of endometrium encountered in 96 per cent of the fifty cases studied. It is not a hyperplastic endometrium but rather an endometrium which denotes the presence of the action of theelin. What has been said leads to perhaps one of the most arresting observations made in this work, namely, *that I never saw a carcinoma of the endometrium in the uterus of a previously castrated individual.*

GENERAL SUMMARY

The activity of the ovary is reflected in the activity of the endometrium. The normal endometrial cycle can be divided into the menstruating phase, a phase of early proliferation, a phase of late proliferation, a phase of early differentiation, and a phase of late differentiation. The four last named phases correspond roughly to the four weeks of the normal menstrual cycle in the order named. The abnormal endometrial cycles, which are owing to abnormal ovarian activity, reflect themselves in arrest of the cycle in any of the phases named above. The phase of arrest is called the persistent phase and the stage of arrest depends on the degree and kind of ovarian dysfunction.

The clinical classification of ovarian dysfunction can be divided into a primary and a secondary group. The primary ovarian dysfunctions are owing to failure in the ovary itself. The secondary dysfunctions are owing to changes in the ovary which accompany or follow failure of the thyroid or pituitary functions. In both groups the histologic manifestations are the same because, as stated, the endometrium reflects only the activity of the ovary.

The study of cystic changes in the endometrium associated with different phases of the cycle indicates that one can separate to some degree the cases of sterility from those of bleeding dysfunction. When cystic changes are present in the proliferative phase of the cycle, the tendency is greatest toward bleeding dysfunction and to a lesser degree toward sterility. On the other hand, when cystic changes are associated with the differentiative phases, the tendency is greatest toward sterility, while the tendency toward bleeding dysfunction is almost entirely absent.

From study of the endometrium associated with carcinoma of the body of the uterus, it would seem that carcinoma occurs practically always in the proliferative type of endometrium, in which there is usually cystic change. This endometrium is not a hyperplastic endometrium but is an endometrium the characteristics of which result from unopposed action of estrin (folliculin) and from absence or failure of activity of the corpus luteum. Even when carcinoma of the endometrium occurs in the preclimacteric state, as it does in approximately a fourth of the cases of endometrial carcinoma, the endometrium usually is of the persistent proliferative type and only rarely is there any evidence of differentiation or of activity of the corpus luteum. The ovaries associated with fundal carcinoma contain cystic portions which probably are the source of estrin in 90 per cent of the cases of carcinoma. Further evidence in support of the view that this endometrium, in which carcinoma occurs,

is attributable to the presence of the action of the estrogenic hormone, is indicated by the presence of estrin in the urine of patients whose uterine fundi harbor malignant growths. This type of endometrium is markedly different from the true atrophic endometrium which results from castration. Carcinoma of the body of the uterus never has been seen as far as I have been able to determine, if an individual has been previously castrated.

It seems reasonable to conclude that the unopposed action of estrin, with its resulting effect on the endometrium, which is a persistent proliferative type of endometrium with cystic change, is the basic principle at work in the development of malignancy of the endometrium of those individuals who possess the genetic factor necessary for the development of cancer. These findings, based on ample histologic studies, seem most significant in view of the growing evidence for the carcinogenic possibilities of estrin-like and estrogenic substances.

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THE BIOLOGIC SIGNIFICANCE OF THE FETAL MEMBRANES*

The Joseph Price Oration

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I PLAN here to discuss the biologic significance of the fetal membranes. My choice of subject was decisively influenced by the fact that questions of biology are at present of absorbing interest over the entire world. This is true not only in matters of scientific research, but also in the predominantly practical branches of medicine.

Surgery today is based on biology, its chief endeavor being to maintain natural functions as far as possible.

It is known that the fetal membranes consist of the amnion and the chorionic membrane. The latter has its origin in the cells of the trophoblast of the fertilized ovum. A digestive ferment produced by these cells enables the trophoblast to penetrate into the decidual layers of the uterus. This biologic activity makes the implantation of the fertilized ovum possible. But to assure the implantation of the ovum is not the only purpose of these cells. At a later stage of the ovum's development, blood vessels connect the embryonic area with the chorionic mesoblast through the allantois and the body stalk. Thus the

*Read (by invitation) at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22 to 24, 1938.

circulation of the villi is established, which at a certain period constitutes the only means of nutrition for the embryo. As we know, parts of the villi later degenerate and form the chorion laeve. Another part, coming into contact with the decidua basalis, undergoes further development. United with maternal tissues it becomes the placenta and serves the nutrition of the fetus throughout gestation.

The chorionic membrane is not the only one of biologic importance during pregnancy. The amnion, the other membrane of the fetus, is equally important. This membrane originates from the ectoderm of the embryonic area through the development of the embryonic sac. In its further development, the amniotic sac extends downward and inward, gradually filling out the uterine cavity. The secretion of the amniotic fluid during pregnancy is one of its most important functions. It is now an accepted fact that the amniotic fluid is produced by the activity of the amniotic epithelium and that it is not the result of the function of fetal kidneys nor of transudation from maternal blood. This is capable of experimental proof. In this connection I may mention the vital staining experiments of Goldmann and Evans. These authors injected pyrrole-blue into pregnant animals. In the mother's internal organs the surfaces became blue, while in the fetus only the skin and the intestinal canal were affected. The amniotic fluid was also blue and the amniotic epithelium pigmented, proving that the dye passed into the amniotic fluid through the amniotic epithelium. The fetus became stained only by swallowing the fluid and by being surrounded by it—no trace of the dye was found in the fetal kidneys or urinary tract.

By the secretion of the amniotic fluid the amnion thus accomplishes one of its most important biologic functions, namely, the protection of the fetus. In addition, through the hydrostatic pressure, it protects the placenta, especially during labor, by preventing serious disturbances in the placental circulation, and also hinders the premature separation of the placenta, which otherwise could easily follow the contractions of the womb.

These functions of the membranes are not all they have to accomplish during pregnancy. Beginning at the fourth month, when the fetus, surrounded by the membranes, already fills the entire uterine cavity, they assume a new function by protecting the uterine cavity and consequently the maternal organism, from the danger of ascending infection by vaginal germs. It is unnecessary here to dwell upon the significance of this function, especially important in cases of prolonged labor. We all know for instance the increased dangers connected with a cesarean section made after the rupture of the membranes. We also know that the danger increases with the time elapsed after rupture. The fact that an increased puerperal morbidity and mortality following premature rupture was observed, led to the overestimation of the dangers connected with premature rupture of the membranes. Quite recently it was still universally believed that the membranes play an important part in the dilatation of the cervix.

The observation has frequently been made that in cases of premature rupture of the membranes the period of labor, instead of being prolonged, is manifestly short. In 1934, at the convention of the Hungarian Society of Gynecologists I published my own conclusions, namely that in cases of premature rupture—where no other anomalies such as contracted pelvis, rigid cervix, abnormalities of presentation or mechanism of labor, etc., exist—the delivery takes less time than in cases where rupture occurred normally. In these cases I not only observed the duration of the labor, and especially the duration of the period of dilatation, but I also counted the labor pains. This is a more correct procedure, as far as the judging of the mechanism of labor is concerned, because it tells the number of contractions of the uterus necessary for the complete dilatation of the cervix, and for the expulsion of the fetus. It was found not only that duration of labor was shorter, but also, and this is more convincing, that fewer pains were necessary for the complete dilatation of the cervix than in cases of intact membranes.

Pataky, one of my collaborators, confirmed my earlier observations. I was sincerely gratified to learn that these facts, to which I had called attention in Europe, had also been proved by various American authors.

This question was also taken up by several other European obstetricians: Guthman, Endres, and, later on, Sunde and Wichmann arrived at the same conclusions and confirmed my findings.

Even at the time I first observed this phenomenon, I raised the question of revising the general belief as regards the importance of the membranes in the dilatation of the cervix. The experiences of American authors, such as Gutmacher and Douglas, and Wilson and Slemons, point in this direction. These observers, having the practical consequences in mind, took a step further and, in order to shorten the time of labor, advocated the artificial rupture of the membranes at the beginning of labor.

Following our observations on the results of premature rupture, Dr. Pataky, my assistant, began to follow up the question of early ruptures, or, in other words, cases in which the rupture occurs after labor pains have started but where dilatation of the cervix is not yet complete. I would like to emphasize the reliability of the diagnoses of early ruptures observed in these cases at my clinic. This, because in all those cases the condition of the external os was determined by vaginal examination. I stress this point because at my clinic vaginal examinations are made only exceptionally in cases where labor does not progress and where no information as to the reasons for this can be gained by external or rectal examination. My experiences, gained from the observation of premature and early ruptures of the membranes, obviously tend to prove that the membranes are not of so great an importance for the dilatation of the cervix as was hitherto presumed. Somebody might ask (as was actually done at the above-mentioned Congress in Hungary), For what purpose did nature, then,

provide the membranes? My answer is: They are here to protect the fetus and the circulation of the placenta, and to keep infection away from the mother. That they also have a biologic significance during labor is shown by those cases of prolonged delivery in which the rupture is premature or early and where, later, the cavity of the uterus becomes infected, as indicated by a rising temperature in the patient during labor, or later, in the puerperium. But this danger exists only in cases where other anomalies are also present. My own experience concerning premature ruptures and the observations on early ruptures by Pataky prove that puerperal morbidity and mortality are on the same level as in other cases, provided that the early or premature rupture is not complicated by other, labor-prolonging anomalies. I do not wish to say, that premature and early ruptures may now be regarded as harmless complications. As confirmed also by our own experiences, they are of no special importance in favoring puerperal infections except in those cases where other anomalies impeding a short labor are non-existent. On the contrary, if there exists another cause for prolongation of labor (contracted pelvis, rigid os, anomalies of presentation or of mechanism of labor), premature and early ruptures should be taken very seriously because, during prolonged labor, numerous possibilities for an ascending infection are present. This fact is also revealed in the paper published on the subject by one of my assistants, Dr. Fátyol. He compared cases of premature rupture of the membranes occurring simultaneously with other complications, with cases in which the premature rupture was the only complication. Not only was the percentage of cases with fever higher (22 per cent) in the former group than in the latter (4.2 per cent) but also the frequency of operations (69 per cent, 3.9 per cent). and the maternal (0.5 per cent, 0.3 per cent), and infant mortality (12 per cent, 0.9 per cent). In any given case it is impossible to know how the labor will turn out. Still less is known in advance about the period of latency, i.e., the time between the moment of rupture and the beginning of labor pains. For these reasons, and in spite of my experience that in cases of simple premature or early ruptures (barring complications) the labor will be shorter, I am partial to a certain conservatism and am not sure about the advisability of rupturing the membranes in order to start labor or to hasten it. Should the labor be prolonged in such a case for some unforeseen reason (weak labor pains, rigid os, etc.), there will be no membrane to protect the uterine cavity from infection and the patient is exposed to grave dangers. On the other hand, and this is a consequence of our convictions, we do not hesitate to rupture the membranes artificially in cases where overdue pregnancy threatens to distort the proportions between fetus and maternal organs, and where labor will not start notwithstanding the administration of the customary medicaments. We also resort to artificial rupturing of the membranes in cases of irregular labor pains during the period of dilatation, in which cases, in our opinion, special indications exist for the rupture.

Here van der Hoeven's observation should be mentioned. He found that in cases where a larger portion of the membranes projects into the os, the dilatation is slowed down and the labor becomes prolonged. If there is only a small amount of amniotic liquor contained within the protruding membranes and the latter are adhering to the external os, the increased contractility of the os may, in Schickele's opinion, lead to a spasm of the os and in spite of the satisfactory pains delivery does not proceed. In such cases artificial rupture of the membranes is indicated.

Having arrived at the conclusion that the membranes have no part in the dilatation of the cervix, or at least a much smaller one than was formerly universally accepted (and still believed by many), the question arises, How is then the process of dilatation to be explained? De Snoo gives a very satisfactory explanation of the part played by the membranes in the dilatation. According to him, the tension at a given part of a sphere is proportionate to the internal pressure and the diameter. Inasmuch as the diameter of the membranes in the cervix, especially at the beginning of the dilatation, is quite small, the tension must be insignificant. This explanation also tends to prove that some factors other than the membranes are responsible for the dilatation. That these factors are not found in the presenting part is shown by those cases where, with high presenting part or even in transverse presentations with ruptured membranes, dilatation will occur. According to de Snoo the dilatation of the os is caused by the activity of the cervix. The contraction of the outer muscular fibers of the uterus during the pains is more complete than that of the internal fibers. Following the contractions of the uterus, the cervix is thus gradually turned to a certain degree.

At this juncture, the results of some recent anatomic research by Stieve must be mentioned. According to his findings the cervix becomes transformed into a cavernous body during pregnancy. The membranes protruding into the cervix flatten this cavernous body and thus dilate the os. This theory seems quite acceptable, but only so far as primiparas are concerned; in multiparas we know that the dilatation of the cervix proceeds in an inward and not an outward direction. In these cases the external os is extended before the internal and therefore the reconciliation of this fact with Stieve's theory of dilatation being caused by the pressure of the membranes on the cavernous body becomes very difficult.

Concluding the discussion of the part played by the membranes in the dilatation of the external os, one may admit some biologic influence of the membranes and also take into account Stieve's theory in cases of primiparas. *But it is also undoubtedly true that the part played by the membranes is only of secondary importance. This, not only because the characteristic mechanism of the dilatation of the external os in multiparas cannot be explained by Stieve's theory at all but, still more, because the question of dilatation is a practical one.* The answer can be founded only on a practical basis, i.e., by observation of

the labor. Those who investigated and observed, just as I did, the phenomena of the dilatation period in cases of premature and early rupture without any other complications, all arrived at conclusions in conformity with my views, maintaining that in the dilatation of the external os the membranes play only a subordinate role. Still, it is perhaps advisable, in view of the skeptics' opinion, to emphasize that the significance of an anomaly can be clearly recognized only if no other complication is present. Just for this reason, the studies touching upon the question of premature and early rupture (and based, I may be permitted to say, on the analysis of antiquated statistical data which do not distinguish between cases with and without complications) are not at all suitable for the solution of this problem.

We see now that the biologic significance of the membranes during the labor lies mainly in the protection of the uterine cavity and of the mother against ascending infections. This gains more pronounced importance only in cases where, on account of other anomalies, labor is prolonged. Our recent experiences and observations show mainly that, in cases without any complications other than a premature or early rupture of the membranes, the first stage of labor becomes shorter than expected.

This observation supports the opinion that the membranes are not so important for the dilatation of the external os as was formerly generally believed and as is still maintained by many. But even in these cases the premature rupture of the membranes may prove disadvantageous on account of the part played by the membranes in hindering the ascending infection. This is especially true in those cases of premature rupture where the so-called "period of latency" is prolonged. That is the reason why we do not, for the induction of labor, employ the artificial rupture of the membranes without careful consideration, in spite of the fact that premature rupture (free from other complications) shortens the labor and lessens the number of uterine contractions. Artificial rupture is very particularly weighed in cases of overdue pregnancy with the slightest disproportion between fetus and maternal organs. If in such a case it should be found later, especially after a prolonged period of latency, that a cesarean section is indicated, the danger to the mother is materially increased.

Having discussed briefly the biologic function of the membranes in pregnancy and labor, I would like to take up the second part of my address, dealing with the biologic functions of the membranes in conditions other than pregnancy and labor. I desire to dwell upon how the membranes, as young tissues of great vitality, could be used in plastic surgery.

One year ago I published the description of three artificially formed vaginas, in which I lined the new-formed vaginal tube with membranes of the fetus. The operation is performed in two stages. One may regard the technique of the first stage, which involves separation of the connective tissues between vagina and rectum, and the forma-

tion of a recess corresponding to the vagina, as fully developed. The lining of this recess with epithelium, the second stage of the operation, may be accomplished by various methods, showing that none of the existing techniques is quite satisfactory. Some authors, Mackenrodt, for instance, lined the cavity with pieces of vaginal tissue taken from other patients following a plastic operation. Others, as Gersuny, Abady, Walter Dannreuther, and Marion Douglas, employ pieces of skin taken elsewhere from the patient's own body. Another technique uses preformed tubes to line the artificial vaginas. Baldwin and Mori, and also Schubert, used pieces of small or large intestine. Some of these operations are imperfect (Mackenrodt, Gersuny, Abady), others are dangerous (Baldwin, Mori), and mainly the methods of Wagner-Kirschner and Schubert can be taken into consideration.

Wagner-Kirschner's method is always preferable on account of its safety. It employs skin grafts (Thiersch) from the thighs. Even if performed by an experienced surgeon, Schubert's method on account of its mortality of 4 per cent should be regarded as a serious operation.

As far as the final results are concerned, Schubert's method has been found superior. Here the epithelial lining of the tube carries a muscular layer, and thus closely imitates natural conditions. The tendency of these tubes to shrink is less pronounced than in tubes prepared according to Wagner-Kirschner's method. I do not intend to discuss the technical details of this operation and wish only to mention some technical drawbacks in connection with Schubert's procedure: Should the intestine, pulled in the anus, slide back, incontinence may result. Fistulas developing between the rectum and the new-formed vagina have been described, as have also abscesses. The rupture of one such abscess may cause a fatal peritonitis. To describe step by step the procedure in lining the artificial vaginal tube with membranes of the fetus would take me beyond the scope of this address. Therefore, I shall limit myself to a summary of my own experiences with this method and, incidentally, bring to your attention one hitherto unknown function of the membranes.

I had the opportunity to examine, nine months after operation, one of the artificial vaginas constructed by me. The inspection disclosed a tube perfectly suited for sexual function. The vaginal secretion was found to contain epithelial cells, leucocytes and Döderlein bacilli. The epithelial cells were decidedly similar to those found in the normal vagina. A bit of tissue was excised from the innermost part of the tube, which shows (Fig. 1) a surface layer of stratified epithelium without a horny layer, just as in the normal vagina. By staining according to Best's method, we found (Fig. 2) that the walls of the artificial vagina also contained glycogen.

The striking appearance of stratified epithelium, replacing the epithelium of the membranes nine months after operation, may be explained in two different ways: Either the stratified epithelium crept in from the introitus into the vagina, or else the epithelium of the

transplant was actually transformed. One may presume that the first explanation fits the case. I remember one of my patients who was operated upon for atresia vaginae. During the operation a hematometra was found with infected, fetid contents. I left the newly formed vaginal tube without a lining, kept open only by tampons. The tube

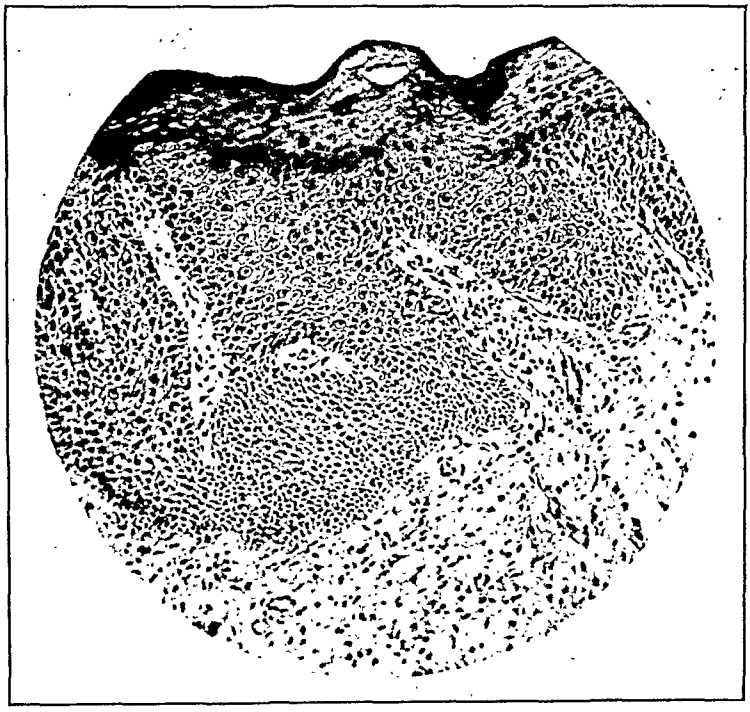


Fig. 1.—The innermost part of the artificial vagina nine months after operation.

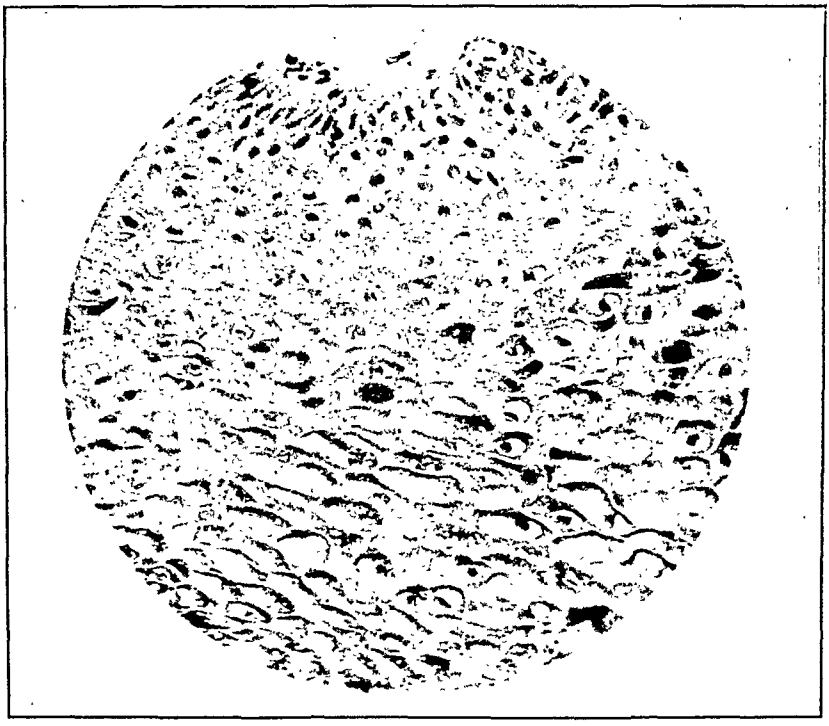


Fig. 2.—The wall of the artificial vagina contains glycogen.

became covered by epithelium in about three months' time. It is improbable that, in those cases where I made a lining from membranes, the epithelization took place in the same manner, because as early as the sixth day we found the membranes adhering perfectly and a smooth tube. The transformation of the epithelium of the membranes appears here to be the most plausible explanation. This is possible because, as we know, the epithelium of the membranes covering the placenta usually consists of two layers, and also because of those familiar little grayish spots in the vicinity of the umbilical cord, the so-called "amniotic caruncles." These show, under physiologic conditions, the same histologic characteristics as the epidermis. It is probable that the amniotic epithelium possesses the faculty of being transformed into the stratified type. That such a transformation may occur in artificially produced vaginas is, to a certain extent, proved by the presence of glycogen, as found by histologic examination. In the amniotic epithelium, glycogen is found under physiologic conditions.

I am aware that there will be contradictions to my statement and doubts as to the transformation of the amniotic epithelium in these cases. Nevertheless, I believe it most probable that the epithelium of the adhering membranes undergoes a transformation in those cases where the operation is performed with adequate precautions to insure sterility, i.e., where the membranes used for lining the tubes are taken from a cesarean section case before rupture of the membranes. My experiences compel me to stress this point. It is quite obvious that the results of such an operation cannot be satisfactory if the membranes delivered through the vagina are used, and still less satisfactory if they are taken some time after rupture and not used immediately after being delivered. The newly formed recess may be regarded as aseptic; an error can be committed only if the membranes used for the lining are not sterile. Obviously, the tube will not remain sterile later on, but then the membranes are already adhering; the important thing is to start the whole process of adhesion under sterile conditions.

To elucidate the question of origin of the stratified epithelium found in the artificial vagina, we performed some animal experiments:

In the first series of these, one eye of a rabbit was enucleated or the conjunctival fold excised. The cavity thus created (or the loss of tissue) was covered with membranes of rabbit fetus, secured by cesarean section. In some cases the membranes adhered to the wound, but these experiments were still not productive of decisive results. It is technically very difficult to work with the extremely thin membranes of the rabbit. In most cases the field of operation became infected. Infection was not the only factor, though very difficult to guard against, which prevented adhesion of the membranes in these experiments. Satisfactory adhesion could not take place under the best of conditions, because these membranes include only a very small amount of chorion.

In another series of experiments pieces of dogs' peritonea were removed and replaced by membranes taken from dogs. Two weeks after the operations there were so many adhesions that we had to count these experiments likewise as unsatisfactory.

The results of the next series were better. A recess was made on the neck of dogs, and this was lined with dog membranes. A section (Fig. 3) shows the opening still present fourteen days after the operation. The microscopic picture (Fig. 4) shows a layer of loose connective tissue moderately infiltrated by leucocytes, separated to a certain extent from a deeper layer of rough connective tissue. The cells of the loose tissue are cuboid, embedded in a network of collagen fibers, and remind one of the connective tissue of the amnion. Some endothelial cells can be seen on the surface.



Fig. 3.

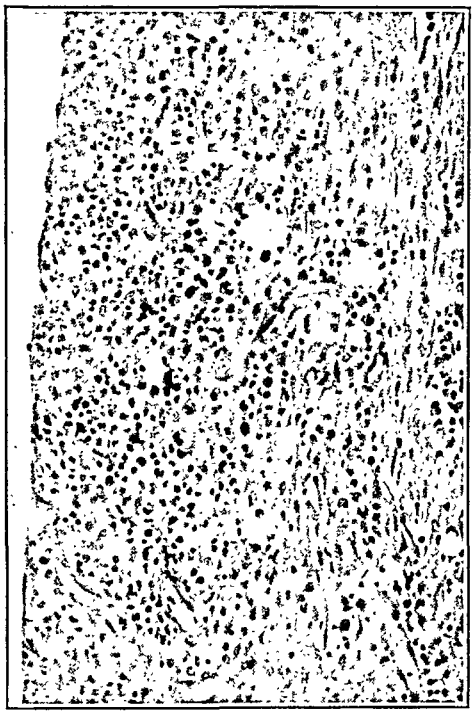


Fig. 4.

Fig. 3.—The recess lined with membranes fourteen days after operation.

Fig. 4.—Loose connective tissue, moderately infiltrated by leucocytes, separated to a certain extent from a deeper layer of rough connective tissue, some endothelial cells on the surface.

Further experiments were carried out on cats: An excised piece of peritoneum was replaced by cat membranes. The conditions found twenty-two days after the operation are shown in Fig. 5. The limits of the transplant are clearly seen, and within these limits are two small, bean-sized, cystlike bodies. Much to our disappointment, the histologic examination revealed the absence of endothelium. The cystlike forms were found to be parts of the transplanted membranes, demonstrating how the latter to a certain extent adhered and lived on.

We also tried to transplant membranes to replace the dura mater in cats. In one of the cases the adherence was satisfactory; still this lone case was not sufficient for the solution of our problem.

After all these unfruitful experiments we concluded that the question could not be answered by animal experimentation.

I approached two of my colleagues, Horvath and Rötth, specialists in diseases of the eye, with the suggestion that they use membrane transplants from the fetus to replace lost conjunctiva in cases of symblepharon. In these cases we also used membranes obtained at cesarean sections, transplanting them as soon as possible after the sections. The results up to the present are very promising. I would like to refer to two of our 6 cases. In a ten-year-old boy, blinded by chalk dust, a symblepharon with corneal scars developed on each eye. The lower lid covered by membrane was free on the tenth day after the operation. A similar case in a woman with contracted symblepharon did not permit the use of an artificial eye. This was successfully operated upon by the same method and the patient now wears an artificial eye.



Fig. 5.—The limits of the transplant on cat's peritoneum, showing two small bean-sized cystlike bodies.

What could not be proved by animal experiments was, thus, demonstrated by operations on the human eye. The fact that in these operations the membranes adhered perfectly, strongly supports, in my opinion, the theory that the epithelium of the transplanted membranes possesses the faculty of being transformed into stratified epithelium. To a certain extent, this would serve as a basis for the experimental production of tissues, so much discussed at present.

Another circumstance supports the view that in cases of artificially formed vaginas the epithelium did not creep in from the outside but was in all probability transformed: A histologic preparation from a case operated upon by Schubert's method is in my possession. This operation was performed in another hospital a year ago. The patient was brought to the surgical department of Dr. Klimko with symptoms of very advanced peritonitis, which proved fatal. Autopsy showed the peritonitis to have been due to rupture of pelvic abscesses. The artificial vagina was taken out and examined: About one-third (the outer third) was covered by epithelium that had crept in from the vulva (Fig. 6). The middle portion of the vagina

possessed no epithelium, and the innermost portion was lined by intestinal epithelium, *not transformed* (Fig. 7).

If the stratified, noncornified epithelium of the walls of the artificial vagina, constructed with the use of membranes, originated from the epithelium creeping in from the outside, then the same thing should have happened here. But nothing of the sort can be found in the intestinal transplant.

That the biologic significance of the membranes lies not only in the possibility of their use in plastic surgery, but that the epithelium of the membranes may also be transformed, is indicated by numerous circumstances. Further experimentation is necessary to enable us to decide whether our cases may really serve as a clinical basis for Spemann's work on tissue induction.

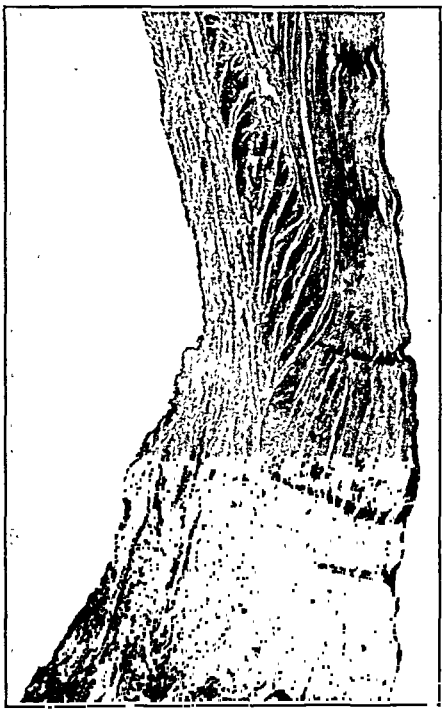


Fig. 6.



Fig. 7.

Fig. 6.—The outer third of the artificial vagina (Schubert) covered by epithelium, the middle portion without epithelium, and the innermost portion untransformed intestinal epithelium.

Fig. 7.—Untransformed intestinal epithelium on the innermost portion of a Schubert artificial vagina.

We have seen how many-sided is the biologic significance of the membranes of the fetus. But in the light of recent observations and new experiences, this significance is not that still generally believed. The membranes by means of the amniotic fluid produced by them, protect the fetus during pregnancy and also shield the mother from ascending infections from the time the egg fills the entire uterine cavity. They likewise prevent premature separation of the placenta. The part played by them in the dilatation of the cervix during labor is not as important as we have believed, and taught up to the present.

Instead of this we are becoming acquainted with perhaps promising possibilities for the use of membranes in the most ideal field of surgical work, plastic surgery.

The results of operations forming artificial vaginas and the success of certain eye operations seem to point in this direction. There is hope that the young tissues of the membranes, endowed as they are with great vitality, can be similarly used in other cases, e.g., for the covering of burns.

BEHAVIOR OF THE BASAL METABOLISM IN THE COURSE OF DEVELOPING TOXEMIA OF PREGNANCY: CORRELATION WITH CHOLESTEROL, PLACENTAL INFARCTS AND RETINAL EXAMINATION*

A Study of 62 Consecutive Adolescent Colored Primigravidas

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IN THE Prenatal Clinic and Lying-in Ward of the Colored Division of Grady Memorial Hospital, we have long been aware of the fact that an unusually high percentage of the cases of toxemia of pregnancy occurs among adolescent primigravidas not over 18 years of age. Upshaw,[1] Colvin,[2] Acosta-Sisson and Baens[3] and numerous other observers have likewise noted the high incidence of toxemia among primigravidas, nevertheless, as Titus[4] has stated, no satisfactory reason has been advanced to explain the predisposing factor of primiparity.

Bearing this fact in mind, it seemed to us that the hidden factors in toxemia are more concerned with the age of the patient than with the question of parity and that if the primigravida is more prone to develop toxemia it is due to the fact that she is usually young rather than the fact that she is carrying her first child. Close observation, therefore, of a group of adolescent primigravidas should afford a better opportunity to discover facts which would throw some light on the etiologic factors concerned in this disease of many theories.

In our previous studies[5-8] we found evidence to support the theory that toxemia of pregnancy is probably due to toxic products of autolysis of acute placental infarcts, which, in turn, are the result of a specific type of vascular disease of the placental arteries brought about by the combined factors of hypercholesteremia of pregnancy and the trauma of fetal movements on the exposed placental vessels.

Since it has long been recognized that hypothyroidism is associated with hypercholesteremia and hyperthyroidism with hypocholesteremia, it would seem that if adolescent primigravidas showed a tendency to

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Springs, W. Va., September 22 to 24, 1931.

hypothyroidism and an exaggerated hypercholesteremia, the latter finding might explain the higher frequency of toxemia of pregnancy in this age-group, through a greater liability to cholesterol-induced vascular change in the placental arteries. Other investigators[11-13] have already noted a greater incidence of toxemia of pregnancy in patients showing hypothyroidism early in pregnancy, but have offered no explanation of the mechanism by which it is produced.

Adolescent primigravidas, registering from time to time in the prenatal clinic during the first trimester of pregnancy, were referred to a special clinic personally supervised by one of us (E. D. C.). In addition to the routine prenatal observations, an initial retinal examination, basal metabolism determination and whole blood cholesterol estimation were made. At intervals of two to three weeks these additional examinations were repeated, and more frequently if any evidence of toxemia appeared.

In this manner it was possible to study the behavior of the basal metabolism, changes in the blood cholesterol and changes in the retinae before, during, and following the development of toxemia, and correlate each with the others and with the clinical evidence of toxemia.

At the time of delivery a specimen of cord blood was saved for cholesterol estimation, and the placenta was prepared and fixed in 10 per cent formalin solution. After fixation for several weeks or more, the placentas were studied as "unknowns" by one of us (R. A. B.)[8] to further verify the fact that the placentas from cases of toxemia show infarcts of the more acute type, whereas placentas from normal cases do not show these lesions.

We are indebted to the Department of Ophthalmology and particularly to Dr. A. V. Hallum for practical instruction given the authors over a period of two years preceding this study, during which time we were acquainted with the ophthalmoscopic diagnosis of the simpler fundamental retinal changes such as edema, changes in the arteriovenous caliber ratio, recognition of angiospasms, arteriovenous compression, increase in arterial light reflex, periarteritis, retinal detachment, and the presence of hemorrhages and exudates. In patients in whom toxemia of pregnancy developed, we availed ourselves freely of consultation regarding the interpretation of questionable lesions and have come to appreciate the immense practical value and importance of retinal examination in the diagnosis and prognosis of toxemia of pregnancy.

Patients who developed clinical evidences of toxemia, were admitted to the hospital for observation. Labor was induced if there was no response to the usual treatment. In spite of these measures three patients developed eclampsia before labor was induced. Six weeks after delivery, a final examination was made, at which time blood pressure, urine, ophthalmoscopic, whole blood cholesterol and basal metabolism examinations were made for comparison with the antepartum findings.

Before discussing the results of the above-mentioned examinations, it should be emphasized at once that the incidence of toxemia of pregnancy in this series of 62 adolescent colored primigravidas was unbelievably high. Twenty-four patients, or 38.7 per cent, became toxic, 9, or

14.5 per cent, showing mild to moderate toxemia, 11, or 17.8 per cent, showing pre-eclampsia, 3, or 4.9 per cent, developing eclampsia, and 1, or 1.5 per cent, developing abruptio placentae.

For the purpose of comparison, 100 consecutive primigravidas from 25 to 30 years of age, from the authors' private cases, were studied, inasmuch as it was found that almost all colored patients in this age period had already become parous. Twenty-one (21 per cent) were found to have developed toxemia, 12 (12 per cent) showing mild to moderate toxemia, and 9 (9 per cent) showing pre-eclampsia. There were no cases of eclampsia or abruptio placentae. It will thus be seen that toxemia occurred nearly twice as often in adolescent primigravidas as in mature primigravidas (Table I).

The results of this study are presented under the subjects of basal metabolism, blood cholesterol, placental infarcts, and retinal changes, following which a correlation of these findings is undertaken, and an effort made to determine wherein these facts support or disprove the theory of the placental origin of toxemia of pregnancy.

TABLE I. INCIDENCE OF TOXEMIA IN ADOLESCENT (13 TO 18 YEARS) AND IN MATURE (25 TO 30 YEARS) PRIMIGRAVIDAS

AGE GROUP	NUMBER OF CASES	MILD TO MODERATE TOXEMIA	PRE-ECLAMPSIA	ECLAMPSIA	ABRUPTIO PLACENTAE	TOTAL NO. TOXIC CASES
13 to 18	62	9 (14.9)	11 (17.8)	3 (4.9)	1 (1.5)	24 (38.7)
25 to 30	100	12 (12.0)	9 (9.0)	0 (0.0)	0 (0.0)	21 (21.0)

BASAL METABOLISM

Talbot and others[9] state that in the female, the basal metabolism increases from the age of 10 to the onset of menstruation. It then falls until, between the fifteenth and sixteenth years, it is 5 per cent below the average trend. They further state that available data indicate that climate and geographic location influence metabolism more than race, as shown in Table II.

We believe, as Litzenberg[10] has already stated, that "deviations from the normal rate must be due to thyroid influence," since the vast majority of patients with hypometabolism responds to thyroid therapy. While the literature on the subject of basal metabolism in pregnancy has become quite voluminous, very little has been published bearing on the subject matter herein presented.

TABLE II. COMPARISON OF BASAL METABOLISM RATES RECORDED BY DIFFERENT OBSERVERS THROUGHOUT THE UNITED STATES*

OBSERVER	LOCATION	AGE	NUMBER OF CASES	DEVIATION PER CENT (WEIGHT)
Talbot	Boston	10-19	87	0
Lucas	San Francisco	8-18	207	− 1
Stark	Wisconsin	9-16	52	− 2
Topper	New York	10-16	39	+ 4
Blunt	Chicago	8-17	58	+ 3
McKay	Ohio	13-18	80	− 7
McKittrick	Wyoming	17-26	100	− 9.9
Stark	Wisconsin	17-20	86	−12
Remington & Culp	South Carolina	18-20	37	−10
Coons	Oklahoma	17-22	99	−16
Hilt	Florida	17-20	46	−11

*Figures are from Talbot, Wilson and Worcester.

Bloss[11] has noticed an increased tendency to toxemia among women who have low metabolic rates early in gestation. He also noted that the placentas from women with hyperthyroidism late in pregnancy, showed much degenerative change with hemorrhage and infarction. Taylor[12] has likewise noted a tendency to eclampsia among women with low metabolism early in pregnancy.

Hughes[13] in studying 1250 basal metabolic determinations in pregnancy, noted a decrease in rate during the second, third, and fourth months, followed by a gradual increase, reaching a maximum in the third trimester. Plass,[14] Baer[15] and others also noted the maximum elevation occurred toward the end of gestation, followed by an appreciable drop in the puerperium. The tendency to a rise in the basal metabolism late in pregnancy has not, heretofore, been suspected of being a part of the clinical picture of toxemia.

TABLE III. AGE DISTRIBUTION OF 62 ADOLESCENT PRIMIGRAVIDAS

13 years	3 cases
14 years	2 cases
15 years	6 cases
16 years	15 cases
17 years	20 cases
18 years	16 cases

The patients in this series, were instructed to eat a light evening meal and take neither food nor liquid from midnight on until the test was made, between 7:30 and 9:30 A.M., preceded by a short rest period. A light portable bedside apparatus was used.

The ages ranged from 13 to 18 years, inclusive, and were distributed as shown in Table III.

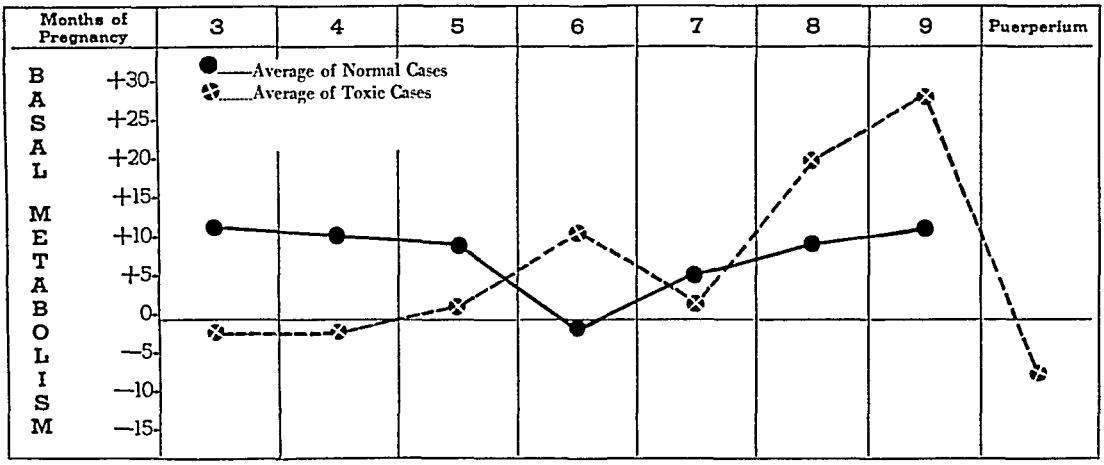


Fig. 1.—Behavior of basal metabolism throughout pregnancy in 38 normal and 24 toxic adolescent primigravidas.

As previously mentioned, 24, or 38.7 per cent, of the patients presented clinical evidence of toxemia of pregnancy. In Fig. 1 the average of the basal metabolic determinations of all toxic and nontoxic cases have been plotted for each calendar month of pregnancy. Unfortunately, for the purpose of comparison we failed to follow the nontoxic patients during the puerperium. However, several observers have previously noted an appreciable drop in the basal metabolic rate in the puerperium.

Analysis of the results showed that the initial basal metabolic rates of the 38 normal cases (solid line and dots) presented variations ranging from plus 2 per cent to plus 18 per cent. The average reading throughout pregnancy, was between plus 5 and plus 16 per cent, except in the sixth month when it showed a substantial drop. With this exception, the curve closely parallels the results obtained by previous investigators.

In the group of 24 toxic cases the initial basal metabolic readings in the third month varied between plus 9 and minus 22, the majority of the readings being between minus 5 and minus 12 per cent. It will be noted that the average basal metabolic rate was less than zero during the third and fourth months, but the individual rates fluctuated over a much wider range than did the normal after the fifth month.

However, without exception, at the onset of clinical symptoms and signs of toxemia of pregnancy, the basal metabolic rate sharply increased to levels far above those previously noted in the earlier months of gestation. The increase in rate varied in individual cases between plus 20 and plus 55 per cent. In some cases an unexplained rise occurred even before well-marked evidences of toxemia were present, making it possible to predict the probable development of toxemia at an early date. Cases which showed a trend in rate from minus 10 in the third month to plus 10 in the seventh month and then suddenly increased to levels of plus 35 to plus 55 per cent, were always associated with severe toxemia, pre-eclampsia, eclampsia, or abruptio placentae. The less pronounced rises to levels of plus 25 to 30 per cent in the eighth or ninth months were usually associated with a less severe degree of toxemia.

It is our impression that the sudden elevation in basal metabolism, accompanying the onset and continuing throughout the course of toxemia of pregnancy, is the result of sudden increase in thyroid activity, brought about by excessive stimulation of the gland by the poisonous autolytic products of acutely infarcted placental tissue.

To determine whether the initial basal metabolic rate at the third month is of any prognostic significance as to the possible development of toxemia later in pregnancy, the cases were divided into four groups: (1) readings of less than minus 10; (2) readings from minus 10 to zero; (3) readings from zero to plus 10; and (4) readings of plus 10 or above. Table IV shows the number of cases and the incidence of toxemia in each group.

TABLE IV. INCIDENCE OF TOXEMIA IN 62 ADOLESCENT PRIMIGRAVIDAS ACCORDING TO INITIAL BASAL METABOLIC RATE DETERMINATIONS AT THIRD MONTH OF PREGNANCY

BASAL METABOLISM	NUMBER OF CASES	NORMAL	TOXEMIA	PER CENT
−22 to −10	4	2	2	50.0
−10 to 0	26	11	15	57.7
0 to +10	20	13	7	35.0
+10 to +24	12	12	0	0.0

In the group showing initial basal metabolic readings of plus 10 or more, there were no cases of toxemia; from zero to plus 10, 35 per cent developed toxemia; from minus 10 to zero, 57.7 per cent developed toxemia; and below minus 10, 50 per cent developed toxemia. The number of cases in the last group is too small to permit accurate conclusions, but with the evident trend to more frequent toxemia, the lower the metabolic rate, it might well be that a larger number of cases would show a still higher frequency of toxemia in this group.

It appears, therefore, that the basal metabolic rate as determined in the first trimester of pregnancy, bears a direct relation to the incidence of toxemia in the last trimester of pregnancy. It also appears that the liability to toxemia is great even though the basal rate is within the limits commonly accepted as normal—minus 10 to plus 10, but that *there is little or no liability to toxemia if the initial rate* is found to be more than plus 10. From a therapeutic standpoint, these findings give promise of great possibilities in the prevention of toxemia, if appropriate treatment is instituted early in pregnancy.

At the present time we are making a study of the effect of adequate doses of thyroid extract in those cases showing initial basal metabolic readings below zero, to determine to what degree toxemia of pregnancy can be prevented.

CHOLESTEROL

As previously mentioned, Hurxthal,[16] Luden,[17] Epstein and Lande,[18] and Mason, Hunt and Hurxthal[19] have shown, by clinical or animal experiments, that in hypometabolic states, the blood cholesterol is increased, whereas in hypermetabolism, it is decreased, and that this inverse relationship holds true whether brought about by pathology of the thyroid gland or by administration of desiccated thyroid.

Turner, Present and Bidwell[20] demonstrated an increase of 19 per cent in blood cholesterol in rabbits, following total thyroidectomy, but the increase was much more marked (137 per cent) in rabbits with experimental hypercholesteremia previously induced by cholesterol feeding. Hunt, Patterson and Nicodemus[21] found the average blood cholesterol elevated in each lunar month of pregnancy, but with variations in individual patients, some showing an unexplained drop in the ninth and tenth lunar months. The administration of thyroid extract caused a drop in the blood cholesterol, which rose to its former level when thyroid extract was discontinued. Dieckmann[22] found no significant difference between the average plasma cholesterol values of a series of pre-eclamptic cases and a series of normal pregnancies, but concluded the values were much higher in the former.

The results of the basal metabolic studies in our series of cases indicated that hypothyroidism definitely predisposed to the development of toxemia in pregnancy. Since hypothyroidism is associated with hypercholesteremia, and hypercholesteremia is the necessary antecedent to cholesterol vascular change in the placental arteries, by which rupture, thrombosis or embolism are produced with resulting placental infarction and toxemia, it was necessary to study the blood cholesterol and correlate it with the basal metabolic findings.

The blood collected for cholesterol determinations was obtained between 8 and 9 A.M. at intervals of two to three weeks with the same preliminary preparation as was mentioned regarding the basal metabolism determinations. The modified Blohr technique was employed for estimation of the whole blood cholesterol. The cases were divided into groups according to whether the basal metabolism was (1) below minus 10; (2) minus 10 to zero; (3) zero to plus 10; and (4) plus 10 or above.

The first group was made up of four patients in whom the basal metabolic rate ranged from minus 22 to minus 10. The incidence of toxemia in this group was 50 per cent (Fig. 2).

It will be seen that the normal cases showed an average initial basal metabolic rate of minus 11 which gradually increased to zero in the eighth month, decreasing to minus 2 in the ninth month. The toxic cases showed an average initial basal metabolic rate of minus 12 which gradually increased to minus 4 in the eighth month but with the onset of toxemia in the ninth month, rose sharply to plus 16.

It will also be seen that the average initial cholesterol value was considerably higher in the toxic (236 mg.) than the nontoxic cases (175 mg.) and, except in the sixth month, remained so throughout. Unlike the other groups to be described, however, it did not drop noticeably in the ninth month in association with the rise in the basal metabolic rate and the occurrence of toxemia, neither did it rise post partum with the fall in basal metabolic rate. As mentioned before, the number of cases in this group is too few to draw worth-while conclusions.

The second group is composed of 26 cases in which the initial basal metabolic rate at the third month, ranged from minus 10 to zero. The incidence of toxemia in this group was 57.7 per cent (Fig. 3).

It will be seen that the normal cases showed an average initial basal metabolic rate of minus 3, which, except in the fifth month, remained minus through the seventh and gradually increased in the eighth and ninth months to plus 12. The toxic cases showed a lower average initial basal metabolic rate of minus 6, which remained minus through the fifth month, then rose steadily each month, reaching a maximum of plus 28 in the ninth month. The increase in the ninth month ranged from plus 22 to plus 55 per cent.

It will also be seen that the average cholesterol value in the nontoxic cases showed moderate fluctuations (171 to 207 mg.), but no definite trend or drop during the eighth and ninth months when the basal metabolic rate was showing a moderate increase. The initial average cholesterol value of the toxic cases (219 mg.) was

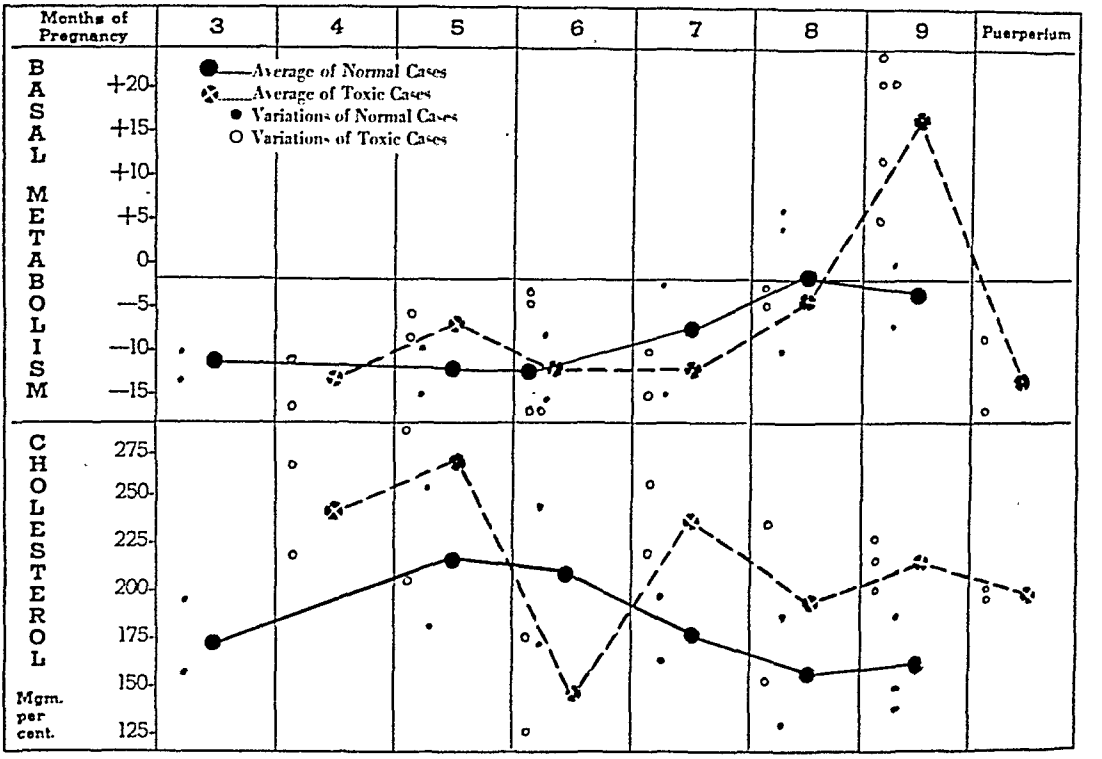


Fig. 2.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 4 primigravidas whose initial basal metabolic rate at the third month was −10 or lower, two of whom became toxic.

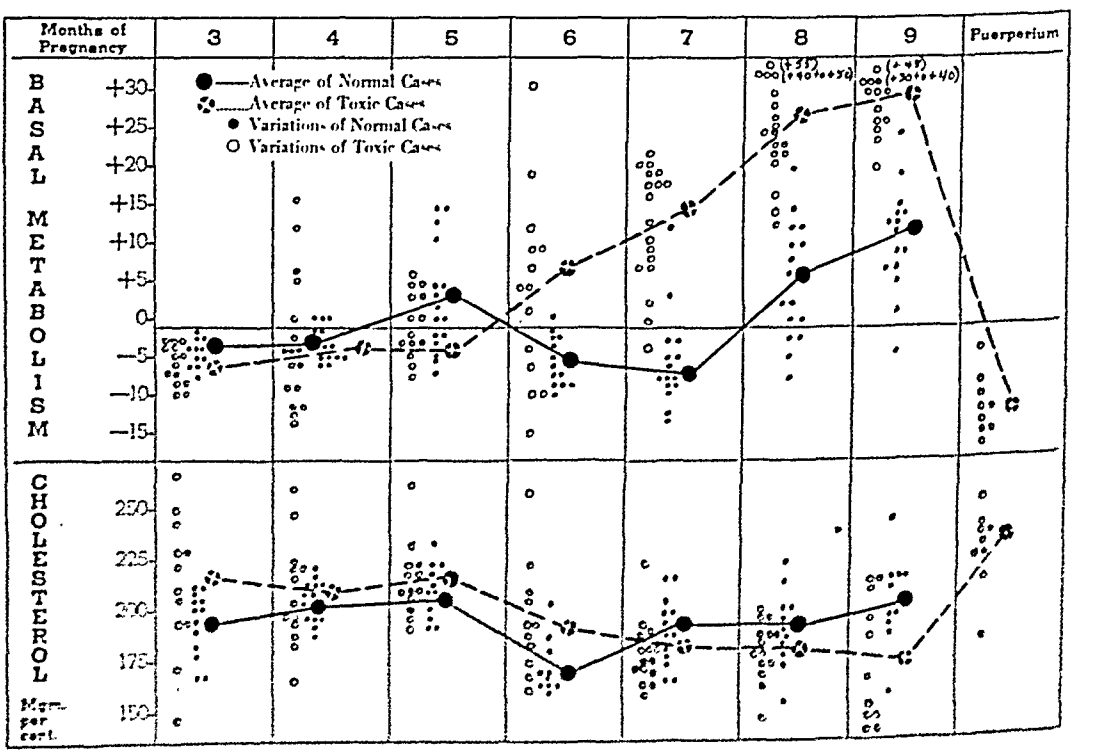


Fig. 3.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 26 primigravidas whose initial basal metabolic rate at the third month was from −10 to 0, 15 of whom became toxic.

considerably higher than that of the nontoxic cases (191 mg.), and showed a definite downward trend to 178 mg. from the sixth month on, during the rise in the basal metabolic rate in association with toxemia. It was necessary to interrupt pregnancy in many of these cases before term.

It will further be seen that with the drop in the average basal metabolic rate of the toxic cases during the puerperium to minus 12, the average cholesterol value rose to 228 mg., even higher than the initial reading.

The reciprocal behavior of the basal metabolic rate and the cholesterol value in the toxic cases, is therefore similar to that which is seen in hyper- and hypothyroid states.

The third group is composed of 20 cases in which the initial basal metabolic rate at the third month ranged from zero to plus 10. The incidence of toxemia in this group was 35 per cent (Fig. 4).

It will be seen that the normal cases showed an average initial basal metabolic rate in the third month of plus 6, which decreased slightly to plus 4 in the seventh

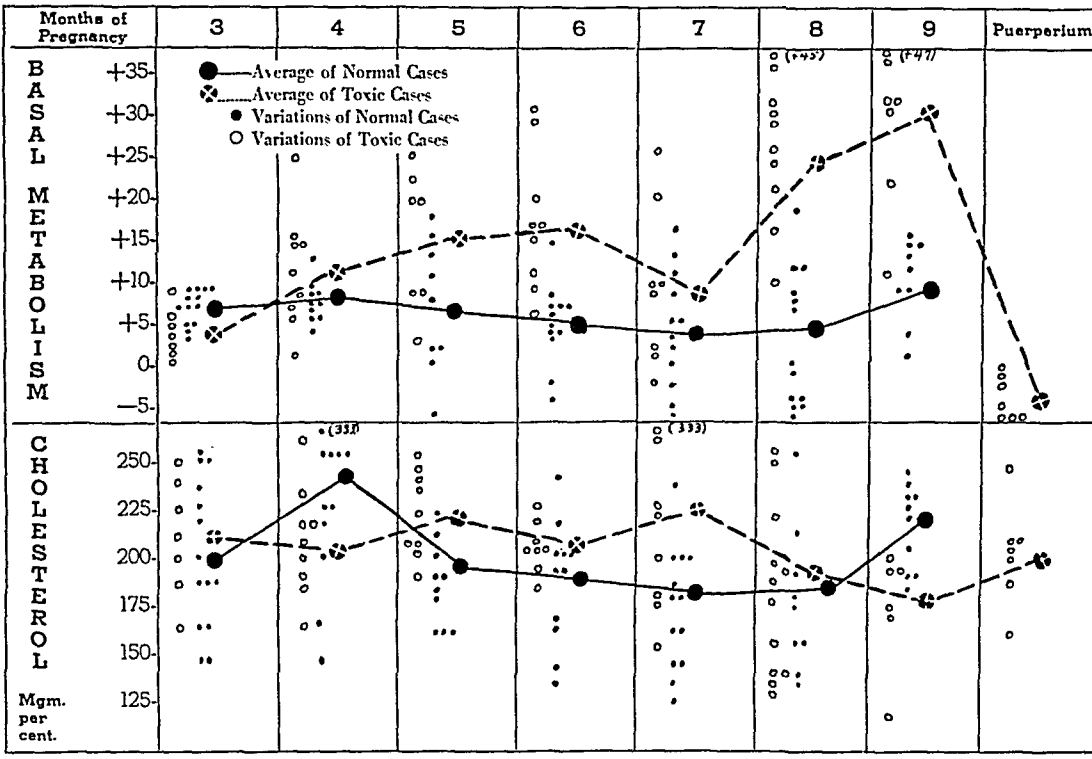


Fig. 4.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 20 primigravidas whose initial basal metabolic rate at the third month was from 0 to +10, 7 of whom became toxic.

month, rising to plus 8 in the ninth month. The toxic cases showed an average initial basal metabolic rate at the third month of plus 4, gradually rising to plus 16 in the sixth month, dropping to plus 8 in the seventh month, then rising sharply to plus 24 in the eighth and plus 31 in the ninth month in association with toxemia.

It will also be seen that the average initial cholesterol value of the nontoxic cases at the third month, of 209 mg. rose to 243 mg. in the fourth month, then gradually dropped to 181 mg. in the seventh month, rising to 193 mg. in the eighth and 218 mg. in the ninth month. The initial cholesterol value of the toxic cases at the third month, of 211 mg. gradually rose in a fluctuating manner to 223 mg. in the seventh month, then dropped sharply to 194 mg. in the eighth and 176 mg. in the ninth month, during the time the basal metabolism was rising sharply in association with toxemia.

It will further be seen that with the drop in the average basal metabolic rate of the toxic cases during the puerperium to minus 4, the average cholesterol value rose 199 mg.

The general trend of the basal metabolism and cholesterol curves in Group 3 (zero to plus 10) is similar to that in Group 2 (minus 10 to zero) and further bears out the similarity in the reciprocal behavior of the basal metabolism and cholesterol to that seen in hyper- and hypothyroid states.

The fourth group is composed of 12 cases, in which the initial basal metabolic rate at the third month was plus 10 or more. None of these patients developed toxemia (Fig. 5).

The initial average basal metabolic rate in the third month, of plus 18, decreased to plus 11 in the sixth and seventh months, rising to plus 22 in the eighth and dropping to plus 15 in the ninth month.

The initial average cholesterol in the third month was 175 mg. and showed no definite trend although there were monthly fluctuations.

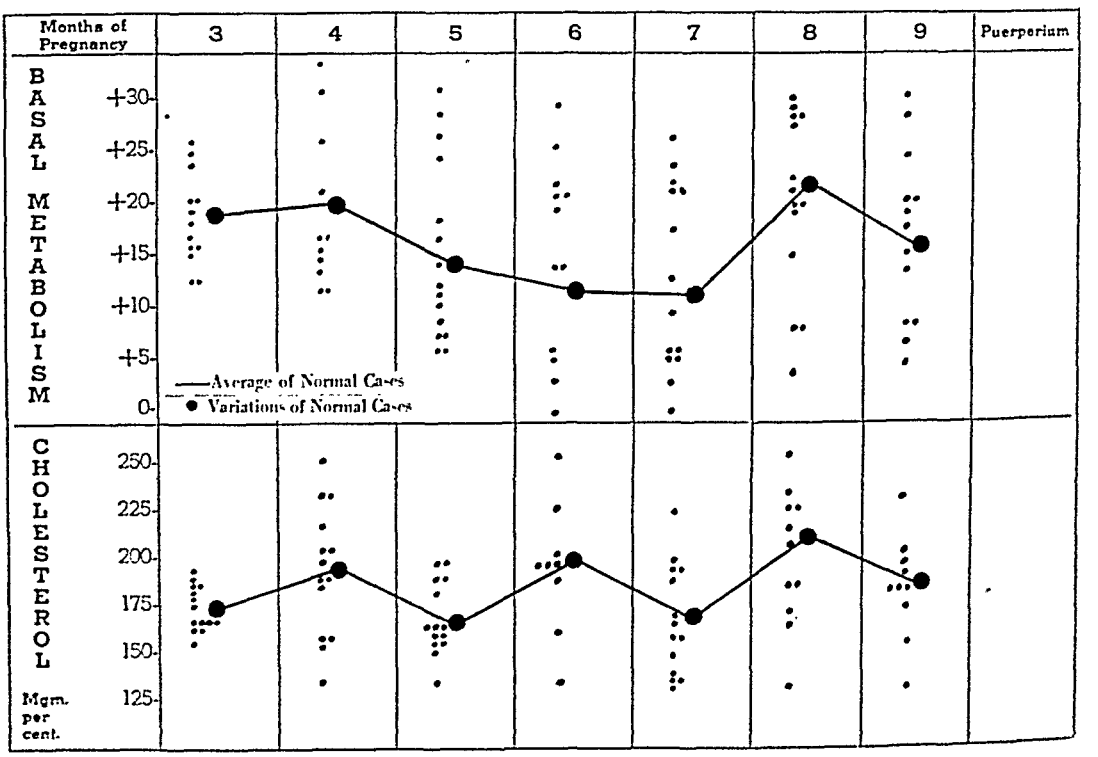


Fig. 5.—Behavior of basal metabolism and whole blood cholesterol throughout pregnancy in 12 primigravida whose initial basal metabolic rate at the third month was +10 or higher, none of whom became toxic.

The average initial whole blood cholesterol at the third month in the four groups is shown in Table V.

In the group showing an initial basal metabolic rate of plus 10 or more (no cases of toxemia), the initial blood cholesterol was 179 mg.; in the group showing zero to plus 10 (35 per cent toxemia) it was 205 mg.; in the group showing minus 10 to zero (57.7 per cent toxemia), it was 204 mg.; and in the group showing readings below minus 10 (50 per cent toxemia), it was 209 mg.

TABLE V. RELATION OF AVERAGE INITIAL WHOLE BLOOD CHOLESTEROL TO BASAL METABOLIC RATE AND INCIDENCE OF TOXEMIA IN 62 ADOLESCENT PRIMIGRAVIDAS

NUMBER OF CASES	WHOLE BLOOD CHOLESTEROL MG. PER CENT	INITIAL BASAL METABOLIC RATE AT THIRD MONTH	INCIDENCE OF TOXEMIA PER CENT
12	179	+10 to +24	0.0
20	205	0 to +10	35.0
26	204	−10 to 0	57.7
4	209	−10 to −22	50.0

While the blood cholesterol values show no significant differences in the groups below plus 10 metabolism, there is a significant drop in the blood cholesterol in the group showing basal metabolic readings above plus 10, in which group toxemia did not occur. This apparently shows that in the presence of hypercholesteremia, the degree of hypercholesteremia is not so important as the factor of trauma of fetal movements on the unprotected arteries on the surface of the placenta, since it has been shown[7] that cholesterol vascular change occurs, not only more rapidly but with less hypercholesteremia if the vessels are subjected to trauma.

The blood cholesterol values in our series are not as high as those presented by Hunt, Patterson and Nicodemus[21] who found an average of 175 mg. at the end of the second month, followed by a gradual increase to 247 mg. at term. Likewise they differ from the statistics of Dieckmann[23] who found in normal pregnancy, an average increase in blood plasma cholesterol of 23 per cent at term. In nonconvulsive toxemia he found values which ranged from 234 to 382 mg. and concluded that there was no significant difference in the level of the blood cholesterol in toxemic and normal pregnant women, but that the values are much higher than in nonpregnant women.

Fetal cord blood was collected at the time of delivery in 58 cases, 35 of which were from normal and 23 from toxic cases. In the normal cases, the cord blood cholesterol ranged from 161 to 189 mg., while in the toxic cases, with only a few exceptions the cholesterol values were lower, ranging from 96 to 133 mg. It would seem reasonable that an increased basal metabolic rate in the mother, in the presence of toxemia, would lower the fetal as well as the maternal blood cholesterol.

It is our belief that the rise in the basal metabolic rate accompanying the development of toxemia is due to excessive stimulation of the thyroid gland from the poisonous autolytic products of acute placental infarcts which result from cholesterol vascular disease in the placental arteries. The increase in basal metabolic rate is in turn accompanied by a drop in the blood cholesterol. This may explain why Slemons and Curtis[24] did not find hypercholesteremia constantly present in eclampsia.

PLACENTAL INFARCTS

The placentas were prepared by removing the membrane, cord and adherent blood, and fixed in 10 per cent solution of formaldehyde for three or more weeks. They were examined by cutting strips 0.5 to 1 cm. in thickness. In order to further test the association of the more acute types of placental infarcts with toxemia of pregnancy, the placentas were studied by one of us (R.A.B.) as "unknowns." It was possible to make a correct diagnosis of the occurrence of toxemia during pregnancy, in 88 per cent of the cases. Except in one case, the errors in diagnosis were due to overlooking very early areas of infarction, rather than diagnosing areas of acute infarction in normal placentas.

In a recent study[8] in which 100 placentas from both normal and toxic cases were examined as "unknowns," it was found possible to classify the infarcts according to the degree of toxemia, and prove the association of a definite placental pathology with toxemia of pregnancy.

Patterson, Hunt and Nicodemus[21] performed complete thyroidectomy on rabbits at the end of the first trimester of pregnancy. Near the end of pregnancy the rabbits developed convulsions and died. Necropsy disclosed toxic nephritis, early toxic hepatitis and pulmonary congestion. The placentas were thicker and darker than normal. On section, beneath the darker surface areas, there were circumscribed black areas, grossly and microscopically characteristic of acute infarcts. The arteries were found to have thickened walls and small lumina and in many vessels the intima was swollen to such a degree by the presence of large fat cells that the lumen was completely occluded.

In the above experiment we do not believe that trauma played a part in initiating cholesterol vascular change in the placental arteries on account of differences in anatomic form and relations in the rabbit's uterus, fetus, and placenta, but of equal, if not more, influence is the fact that the rabbit is an animal peculiarly unable to handle or metabolize cholesterol. Hence, an unusual degree of deposit occurs in the arteries, leading to occlusion and infarction.

In previous experiments[5] we demonstrated that repeated injections of autolysate of placental tissue into guinea pigs produced convulsions and pathologic evidences of toxemia. Injections of autolysates of other tissues caused clinical and pathologic evidences of toxic effects from protein split products, but none of the animals developed convulsions.

The question arises, what is there in the autolysate of placental tissue which causes convulsions to occur in the rabbits or guinea pigs, and why do convulsions fail to occur when the animals are injected with autolysate of other tissue?

We believe the answer to this question is found in the fact that placental tissue differs from all other tissues in its high content of arginine. This amino acid is apparently a necessary component of any tissue which is undergoing rapid growth or has to do with growth. Considering the rapid growth and function of the placenta, one might expect to find that arginine represented a larger percentage of the nitrogen than in other tissues.

Harding and Fort[25] in analyzing placental tissue for its nitrogen components, found that arginine made up 24.08 per cent of the total nitrogen, a strikingly high value which is about twice that of any other tissue. Graff and Graff[26] studying 10 mature placentas found an average arginine nitrogen value of 14.9 per cent. They quote the work of Ehrenberg and Lievenov, who obtained a value of 21.3 per cent. They state that Wehefritz, who found values of 22.8 per cent in a five months' placenta and 13.9 per cent in a nine months' placenta, agreed with Ehrenberg in stating that the arginine content decreases with the age of the placenta.

We believe that the high content of arginine in placental tissue explains the peculiar eclamptogenic power of this tissue through the probable liberation of guanidine from arginine by a series of oxidation reduction reactions during autolysis as described by Parker[6] working with one of us (R. A. B.).

A consideration of the physiologic and pathologic effects of injection of guanidine, cannot fail to impress one with the fact that the symptoms and findings strikingly resemble those found in pre-eclampsia, eclampsia, and abruptio placentae. Titus and others[27] in a summary of the outstanding effects of guanidine intoxication list them as follows: disturbance in carbohydrate metabolism; fluctuation in blood sugar (hypoglycemia); increase in blood uric acid, amino acids, and lactic acid; increase in blood pressure; edema; renal damage and convulsions. To these may be added peripheral vasoconstriction, demonstrated by Major[28] and others.

Several investigators have described the presence of an increased amount of guanidine in the blood of pre-eclamptic and eclamptic women. Minot and Cutler[29] found guanidine concentrations of 0.50 and 0.85 mg. in pre-eclampsia and eclampsia as compared to 0.25 to 0.40 mg. per 100 c.c. of blood in normal pregnancy.

Andes and others[30] found the blood guanidine value in mild toxemia the same as in normal pregnancy, but in severe toxemia there was an additional rise which persisted as long as the toxemia existed. These authors, studying the whole blood guanidine values of 17 normal pregnant women, found an average value of 0.23 mg. In studying the whole blood guanidine values of eight women during the puerperium, they found the average value elevated in every case to almost twice that observed before delivery. This post-partum hyperguanidinemia begins soon after delivery, increasing to a maximum between the third and seventh days, then decreasing gradually to a normal level by the end of the third week.

In our opinion, the probable source of post-partum hyperguanidinemia is autolysis of remnants of villi and the involution of the uterus which progresses so rapidly early in the puerperium.

Although Malmejac[31] arrived at conclusions similar to those of Andes,[30] de Wesselow,[32] and Stander[33] have expressed dissenting opinions concerning the presence of hyperguanidinemia in women with toxemia of pregnancy.

We are not qualified to pass judgment upon the explanations offered for variations in results obtained by different observers, but some of the differences may possibly arise from the fact that the concentration of guanidine in the blood of a toxic patient may vary from time to time according to the amount probably liberated in the blood stream. Experiments have shown that a given amount injected slowly may not be demonstrable in the blood, or produce recognizable effects, but the same amount injected rapidly, produces definite effects and shows increased con-

centration in the blood. If autolysis of acutely infarcted placental tissue is the source of guanidine, as we believe, it is possible that variations in the rate of autolysis may account for lack of uniform results by different observers.

In recent years the discovery that retinal vascular spasm is a frequent finding in association with toxemia of pregnancy, has led to widespread acceptance of the theory that toxemia of pregnancy is a disease of the smaller terminal arterioles and that pathology in the liver and kidney and other organs is secondary to vascular disease. Volhard[34] advanced this theory in 1918. Since then other investigators have expressed themselves in favor of this concept. Irving,[35] Eastman[36] and others conclude that arteriolar spasm is the common factor in toxemia of pregnancy and a clear understanding of the nature of this disease awaits a satisfactory explanation of the cause of arteriolar spasm.

Recent studies have shown that the elevation of blood pressure following injection of guanidine, is due to peripheral vasoconstriction of the smaller arterioles. Barksdale[37] injecting sublethal doses of dimethyl-guanidine sulphate into the peritoneal cavity of the frog and rabbit, noted arteriolar constriction in the frog's foot and the rabbit's ear within four minutes, followed by a return to normal arterial caliber within twenty minutes.

Major[28] sought to determine the mechanism of vasoconstriction following guanidine injection. He ruled out the heart beat as a factor in the associated hypertension, by cutting the vagi, without influence on the blood pressure. As added proof, he registered the contractions of the ventricles and auricles, and noted the carotid blood pressure. The viscosity of the blood was studied, with negative results. Finally, to determine the influence of the central nervous system, the medulla of a dog was removed, followed by injection of guanidine. The blood pressure rose, just as in the nondecerebrated dog. From these studies he concluded that guanidine caused vasoconstriction and hypertension through direct action upon the musculature or the nerve endings in the arteriolar wall.

This work lends support to our belief that the elevation of blood pressure in toxemia of pregnancy, is due to peripheral vasoconstriction of the smaller arterioles, as a result of the action of guanidine directly upon the musculature or nerve endings in the vessel wall.

STUDY OF THE RETINAE

Mylius[38] Wagener[39] Hallum[40] and Mussey[41] have demonstrated that toxemia of pregnancy is associated with spasms and tonic constrictions of the retinal arteries; that the constrictions disappeared if the blood pressure dropped, but became fixed and generalized if it remained elevated and the toxemia persisted; that prolonged severe constriction was followed by localized edema or hemorrhage in the adjacent retina and that if the spastic lesions disappeared with the termination of pregnancy, the blood pressure dropped to normal but where organic vascular lesions remained, the blood pressure was persistently elevated. Corwin and Herrick,[42] Peckham,[43] and other observers, in follow-up studies of women whose pregnancies were complicated by toxemia of pregnancy, have emphasized the causative relationship between toxemia of pregnancy and chronic vascular and renal disease.

In 24 cases in our series, ophthalmoscopic examinations of the retinae were made at the onset and during the course of toxemia. Fifteen of these cases were further studied six weeks after delivery. There were three cases of eclampsia and one of abruptio placentae, and in every case, localized and elongated retinal arterial spasms along with generalized constriction of one or more of the major arterial branches, were seen. On retinal examination of these cases six weeks after confinement, one, an eclamptic, presented a normal retina; the remaining three showed evidence of variations in the caliber of the arteries and increased light reflex over the involved portion of the vessels. No hemorrhages or exudates were found during or following pregnancy. The majority of the spasms and retinal changes occurred within a radius of 2 to 3 disc diameters from the disc.

There were 11 cases of pre-eclampsia and in every case changes in the arterial caliber were seen. These changes varied from occasional localized arteriolar spasms, changeable in location or size from time to time, to extensive constriction of one or more arteries. With persisting and increasing toxemia, the sharply localized

spasms changed to spindle-shaped spasms, which, in turn, elongated until the greater part of the length of the artery was involved. In a few of the more prolonged, advanced, cases of toxemia, it was observed that the entire arterial tree became so involved by generalized constriction that it presented a picture of chronic vascular disease rather than that of true toxemia of pregnancy. If the observer, therefore, views the retinal vascular pattern for the first time, after long-standing toxemia has brought about generalized constriction, he may interpret the picture as one of chronic vascular disease. The greater severity of the toxic symptoms, however, will aid in the diagnosis of advanced toxemia. No hemorrhages or exudates were seen in these cases.

Seven of the 11 pre-eclamptic patients reported for examination six weeks after delivery. Four patients presented normal retinae, but in the remaining 3, the arteries were definitely damaged as was evidenced by persistent variations in arterial caliber, increased light reflex over the constricted portions of the vessels and disturbance in the arteriovenous ratio.

Of the 9 cases showing mild to moderate toxemia, 6 presented localized arteriolar spasms. The remaining 3 showed no demonstrable change, except that suggestive elongated constrictions appeared in one or more branches in 2 of these cases, but promptly receded and disappeared when labor was induced.

Four of the 9 mild to moderately toxic patients returned six weeks after delivery, and the retinae were found to be normal in all cases.

In reviewing the charts of the toxic cases, we were impressed with the fact that the degree of involvement of the retinal arteries closely paralleled the clinical aspects of the toxemia and the behavior of the blood pressure. As the toxemia increased, the sharply localized spasms increased in number, then became spindle-shaped and lengthened until finally the appearance was that of generalized constriction, the arteriovenous ratio changing from a normal of 2 to 3, to a ratio of 1 to 3 or 4. The elongated constrictions generally showed a marked pallor of the vessel wall. As the spasms increased in number and the vessels began to show generalized constriction, there was a progressive rise in blood pressure.

It has been our observation that once the local or spindle-shaped constrictions progress to a state of generalized constriction, the blood pressure is slow to decrease during the puerperium. Herein lies the danger of prolonged or expectant treatment of the more severe toxemias, inasmuch as it may lay the basis for chronic vascular disease.

It will be noted that in all cases of severe toxemia, changes in the caliber of the retinal arteries were consistently found. This is exactly what one would expect to find, since hyperguanidinemia is known to be present in cases of severe toxemia, and the action of guanidine is thought to be on the nerve endings or directly on the muscle of the arteriolar wall. If ophthalmoscopic examination was made a part of the obstetrician's examination in every case of toxemia, the uniformity and consistency of the finding would be amply demonstrated. While dilatation of the pupil is necessary for a thorough study of the retina, much can be learned by simple examination without drops, if the room is darkened. In this way, changes in certain arteries may be followed more closely.

SUMMARY

To summarize, therefore, the foregoing investigations in this series of adolescent primigravidas indicate that toxemia of pregnancy is not only much more frequent in hypothyroid gravidas and in adolescence, but is much more severe, and that emphasis should be placed upon youth rather than nulliparity as a predisposing factor in toxemia of pregnancy. They further show that the accepted relation of high blood cholesterol values to low basal metabolic rates and vice versa, also applies during the state of pregnancy and that when toxemia develops, the thyroid is apparently stimulated to greater activity, and responds in a manner apparently similar to its behavior under the influence of other intoxications, by a sharp rise in the basal metabolic rate.

They further demonstrate that the more severe forms of toxemia of pregnancy are associated with the more acute types of placental infarcts and that as toxemia develops and increases, spasms appear in the retinal arteries and grow more numerous and severe until a state of generalized retinal arterial constriction is produced. The degree of involvement of the retinal arterioles parallels the rise in blood pressure and is probably a measure of the involvement of the arterioles throughout the body.

DISCUSSION

Many theories have been proposed to explain toxemia of pregnancy, but until it is recognized that placental infarction is the probable basic factor, we do not believe that any of these concepts will fit into the picture. A theory is more likely to prove to be correct if it is built up, step by step, by correlation of the outstanding clinical and pathologic manifestations of the disease.

The theory proposed by one of us (R. A. B.) to explain toxemia of pregnancy, had its inception in the clinical observation of the frequent association of the so-called "red infarct" on the surface of the placenta in cases of abruptio placentae. Routine examination of placentas extending over a period of ten years during which several thousand were examined, demonstrated the fact that infarcts of the more acute type were consistently found in cases of pre-eclampsia, eclampsia, and abruptio placentae. It became possible to classify infarcts[8] and correlate them with the severity of the toxemia, so that one might predict the type of infarct which would be found in the placenta; or by examination of an "unknown" placenta, one might state whether the patient was normal or toxic.

Microscopic examination of acute infarcts showed necrotic villi with open intervillous circulation, through which the same maternal blood coursed as between the healthy villi just across the border of the infarction. This finding alone disproved the frequently quoted statement that the infarct was the result of the toxemia and not the cause. Manifestly a hypothetical toxin in the maternal intervillous blood, of sufficient toxicity to cause necrosis, could not have a selective action on a certain group of villi, and be harmless to the villi surrounding the infarct. The presence of thrombi in the villous vessels in the infarcted area indicated that necrosis resulted from interruption of the fetal vessels rather than in the maternal sinuses.

The question then arose, as to the cause of interruption in the villous circulation. The frequent finding of yellow-white deposits of fibrin on the fetal surface of the placenta, beneath the amnion, and the occasional finding of a thick layer of fibrin covering a considerable part of the fetal surface, as in Fig. 5 of the previous article[5] indicated that extravasations of fetal blood frequently occurred on the fetal surface of the placenta and were probably due to rupture of a fetal vessel from the trauma of vigorous fetal movements. It seemed reasonable that from rupture, thrombosis at the site of injury, or embolism, infarction of the dependent placental tissue must have occurred.

A definite predisposing cause of infarction came to be recognized in the discovery of the fact that the medium sized or small placental arteries

occasionally showed a localized accumulation of large transparent cells beneath the endothelium either surrounding the lumen to produce concentric narrowing of the vessel or massed on one side to cause an excentric narrowing of the lumen.[7] These cells were recognized to be morphologically similar to the large fat cells described by Leary[44] in artificially produced cholesterol vascular change in rabbits and also similar to those seen in human coronary thrombosis. It seemed reasonable to believe that in the presence of hypercholesteremia of pregnancy, the trauma of vigorous fetal movements on the unprotected arteries on the fetal surface of the placenta was both a predisposing cause of focal cholesterol vascular change, and also an exciting cause of rupture, thrombosis or embolism after focal cholesterol change had taken place.

Granting the definite association of the more acute types of placental infarcts with toxemia of pregnancy and the occurrence and predisposing influence of cholesterol vascular change and fetal trauma as the etiologic factors in placental infarction, a question still remained as to how the poisonous protein split products of autolysis of the infarct, produced the manifestations of toxemia of pregnancy and convulsions.

It seemed rational to explain the peculiar eclamptogenic nature of autolyzed placental tissue on the basis of its high content of arginine from which guanidine theoretically, might be obtained by a series of oxidation reduction reactions, as shown by Parker.[6] Further work is being done, to show, by chemical proof if possible, that a greater amount of guanidine may be obtained from placentas than from other tissues.

The fact that the placenta contains a higher content of arginine in the fifth, sixth, and seventh months than at full term may be of considerable clinical significance. With liberation of greater amounts of guanidine at this stage, one might expect toxemia to be more fulminating and show higher blood pressure and greater frequency of convulsions. Our clinical impressions bear out this suggestion.

Post-partum hyperguanidinemia may not be sufficient to raise blood pressure or produce convulsions after normal pregnancy, but when superimposed on the pre-existing hyperguanidinemia of pregnancy complicated by toxemia, the combined effect may be sufficient to produce late post-partum convulsions, which are known to occur as late as the seventh to tenth day after delivery and which have always seemed to be a stumbling block to any theory of the cause of eclampsia.

It is altogether possible that this finding explains another phenomenon which is often seen after delivery in patients in whom toxemia has existed for some time late in pregnancy. Following delivery of the patient one expects the blood pressure to fall, but in many cases it rises daily, reaching a maximum level as late as seven to ten days post partum. A marked rise in blood pressure within the first week after delivery, therefore, is not without significance and may indicate the possibility of post-partum eclampsia. It is altogether possible that the physiologic post-partum hyperguanidinemia may explain the headaches which occur so frequently in normal cases the first week following delivery.

The antagonistic effect of liver extract on guanidine may possibly explain some of the paradoxical findings which are seen in those cases of

abruptio placentae associated with toxemia. Except for the greater frequency of the infarction on the maternal surface of the placenta in cases of abruptio placentae, the placental lesions of eclampsia and abruptio placentae are the same. In abruptio placentae, however, there is a definitely increased incidence of shock with sudden fall in blood pressure and often a hemorrhagic tendency, not only in the uterus but elsewhere in the body. Unlike eclampsia, there is very little tendency to convulsions.

Is it possible that abruptio placentae is the expression of a greater degree of liver damage, than takes place in eclampsia, thereby subjecting the patient to liver extract of her own making? The drop in blood pressure, tendency to shock, and hemorrhage and the rarity of convulsions strongly suggest that this is the case.

Certain practical deductions may be made from this study. It is quite apparent that illegitimacy and nulliparity, do not predispose to toxemia of pregnancy on the basis of worry or the mere fact of nulliparity, but rather on account of the fact that these patients are usually adolescent or in early maturity. Since pregnancy in the very young, carries with it a greatly increased danger of toxemia, it would seem that this might well be taken into account, in the question of very early marriage.

Vorzeimer and others[45] advocated more watchful prenatal care for those patients who presented stigmas of endocrine disturbance and low metabolic rate, on account of the increased liability to toxemia. It would seem necessary to supervise adolescent primigravidas in the same watchful manner and for the same reason. The influence of geographic location, early marriage, or diet may have more to do with statistics on maternal mortality in some sections than a supposed inferior quality of prenatal care.

It would seem advisable to determine the basal metabolic rate of each new patient, early in her pregnancy, likewise the blood cholesterol estimation. If these tests indicate hypometabolism, sufficient thyroid extract should be given to bring the basal metabolic rate to a plus reading, without causing over-stimulation. The possible advantage of this treatment is to lower the blood cholesterol and lessen the tendency to cholesterol vascular change in the placental arteries. Should toxemia develop, notwithstanding this measure, further use of thyroid extract would seem to be contraindicated, since the thyroid is already becoming overactive. There is no indication for Lugol's solution, since attention should be directed to termination of the pregnancy, rather than to the overactive thyroid gland.

Although the behavior of the basal metabolism at the onset and during the course of toxemia would appear to furnish another sign of impending toxemia, we do not believe that this or any other test at the present time, is equal to the blood pressure in reliability or simplicity.

CONCLUSIONS

1. Adolescence is an extremely important predisposing cause of toxemia of pregnancy, and is a much more important factor than parity.

2. Adolescent gravidas with basal metabolic rates of plus 10 or more show little or no elevation of blood cholesterol and apparently are not so liable to toxemia.

3. Adolescent gravidas with basal metabolic rates below plus 10, show hypercholesteremia and are increasingly subject to toxemia as the basal metabolic rate decreases.

4. The high incidence of toxemia of pregnancy in cases whose basal metabolic rates are within a range commonly accepted as normal and who show only moderate hypercholesteremia emphasizes the importance of the trauma of fetal movements as the probable predisposing cause of cholesterol vascular change and the exciting cause of thrombosis in the placental arteries.

5. During the course of developing toxemia, there occurs a sharp rise in the basal metabolic rate, associated with a drop in the blood cholesterol.

6. During the puerperium of toxic patients, the basal metabolic rate falls to, or below its former low level and the whole blood cholesterol rises to or above its former high level.

7. By examination of placentas as "unknowns," it is possible to correctly diagnose the occurrence of toxemia during pregnancy in 85 to 90 per cent of the cases.

8. Spasms and constrictions of the retinal vessels are consistently found in all cases of severe toxemia and parallel the severity of toxemia and rise in blood pressure.

9. The high content of arginine in placental tissue is the probable source of hyperguanidinemia in toxemia of pregnancy, through autolysis of acute placental infarcts.

10. Hyperguanidinemia is the probable explanation of vascular spasms and the clinical and pathologic evidences of toxemia of pregnancy.

11. The possibility of preventing cholesterol vascular change in the placental arteries, by administration of adequate doses of thyroid extract during pregnancy, and restriction of cholesterol-containing foods, would seem to be the most effective measures of prevention of toxemia of pregnancy.

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DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—I wish to emphasize one point, especially, that is the easy clinical application of the procedures advised. We know the value of prenatal care. This paper adds another valuable method of detecting the probability of toxemia of pregnancy early in pregnancy.

It has been demonstrated by many authors that in normal cases of pregnancy the basal metabolism gradually rises to plus 10 or 15, possibly a protective mechanism. These authors demonstrated that if a woman has a basal metabolism of plus 10 or more she will not develop toxemia, but if the metabolism be low in early pregnancy, 50 per cent or more of the cases will later develop toxemia. So this paper adds a feature of prenatal care, which by a simple method permits dividing our cases of pregnancy into three groups, namely: first, those unlikely to have toxemia; second, those who, probably, may have toxemia; and, third, those who are almost sure to have the toxemia of pregnancy.

DR. LESTER A. WILSON, CHARLESTON, S. C.—With the high incidence of toxemia reported in this paper we can agree. From a series of 1,000 unselected cases in private practice our incidence of toxemia was 20 per cent. Of this number 6.2 were severe enough to necessitate terminating the pregnancy.

In a recent study of 3,909 admissions to our ward service at the Roper Hospital, 9 per cent of the cases were toxic; 2.8 were eclamptic. It is our belief that toxemia occurs more frequently in certain areas of the South than elsewhere.

The evidence presented does not show, in my opinion, satisfactory proof that placental necrosis resulting in hyperguanidinemia is not the result of some other agent or toxin rather than the cause of the toxemia. If trauma from fetal movement is a factor in producing toxemia why has not a picture similar to eclampsia in human beings been demonstrated in animals?

DR. HERMAN W. JOHNSON, HOUSTON, TEXAS.—In 1927, 1928, and 1929 Dr. H. O. Nicholas, Head of the Department of Biochemistry of Rice Institute, Dr. Robert Johnston, my associate, and I presented papers before the Texas State Medical Association on the amines as the etiologic cause of eclamptic toxemia.

We argued that the source of the toxin was definitely in the placenta, otherwise it would be difficult to explain the following facts: why the presence of a placenta is absolutely necessary to the production of pre-eclamptic toxemia; why symptoms improve when absorption from the placenta ceases with lowered intrauterine pressure, following death of the fetus and with fairly rapid absorption of amniotic fluid; also why improvement follows rupture of the membranes.

We argued that circulatory obstruction in the placenta was necessary for the production of the toxin, and this obstruction is brought about by several important factors: (1) The embryonal nature of the tissue and blood vessels of the placenta

predispose it to apoplexy, obstruction, and trauma from violent fetal movements; (2) The actual circulatory accident is precipitated by factors having to do with increased intra-abdominal pressure. The human female is the only animal that suffers from eclamptic toxemia and about the only thing she does which no other animal does is to maintain the upright position. The other conditions predisposing to circulatory damage in the placenta are all decidedly those of pressure, first pregnancies, twins, polyhydramnion, overweight of babies.

We must give the credit to Young of Edinborough for being the first to insist on the relationship between placental infarction and eclamptic toxemia. He thought the toxic substance a split protein. When the circulatory obstruction takes place, infarction may be small, massive, or diffuse and nondiscernible macroscopically. Deprived of nourishment the placental cells may be then reduced, by the cell ferments, to their amino-acid content. Among the amino-acids possible of formation would be histidin, tyrosin and arginine, because they are present in placental tissue. Dr. Nicholas found that tyrosine represented 4.26 per cent of the dry weight of placenta. It is apparent that these amino-acids formed in the placenta would hardly be toxic even if absorbed rapidly, because the blood stream has a buffer system to dispose of them as indicated by the constancy of its amino-acid nitrogen. If however these amino-acids of the placenta are converted into their respective amines and then absorbed, they are toxic and continue so until deaminized. The amount of tyrosine in even a small area of infarction if converted quickly and absorbed quickly could be lethal. Hanke and Koessler showed that under certain conditions amino-acids were converted into amines by enzymes of numerous strains of *B. coli*, and later found the same faculty was possessed by various strains of *Streptococcus hemolyticus*. To date there are about eighty organisms with this faculty. This explains the increased incidence of toxemia, in pyelitis, late pregnancy when permeability of large bowel mucosa is increased, respiratory epidemics, etc.

Chemical examinations were made when possible of vomitus, blood, urine, and placenta. We thought at first that histamine, the typical endothelial toxin, which secondarily through the adrenals produces a pressor effect, was the offending amine. All examinations were negative for histamine. Examination for tyrosine was then made and in practically all specimens where the toxemia was marked tyramine was found in the vomitus, urine, blood, and placenta. No tests were made for guanidin, as at that time the test was not very conclusive, and, too, guanidine was thought to be much less toxic.

Tyramine chemically and pharmacologically is quite similar to adrenalin and thyroxin. It has a strong pressor base and accounts very well for milder forms of hypertension in late pregnancy; for pre-eclamptic toxemia; and in the allergic individual where capillary spasm is also produced, for eclamptic toxemia. Capillary spasm, edema, and convulsions are probably allergic reactions to the causative amine. Necessarily the question is more involved than this—other amines, liver function, and parathyroid function, may play an important part in what happens to the patient.

A decade has now passed and we still believe that tyramine is the important amine in the causation of toxemia of late pregnancy.

DR. CARL HENRY DAVIS, WILMINGTON, DEL.—At the Dallas, Texas, meeting of the American Medical Association in 1926, I reported the results of my first study on the changes of thyroid function during pregnancy as evidenced by changes in basal metabolism. Contrary to most reports then in the literature it was found that if a woman with a normal thyroid had adequate iodine during pregnancy her basal metabolism remained almost stationary and within normal limits. A group of 16 women who had thyroid hypertrophy all had an elevation of the basal metabolism above normal limits even though they took iodine. In connection with Dr. Colvin's observations it is interesting to note I had four patients in the group studied who had late toxemia of pregnancy; all had low readings and two were below minus 10 per cent late in pregnancy (J. A. M. A. 87: 1004, 1926). In a later series of one hundred consecutive pregnant women seen at my office early in pregnancy, it was found that 33 per cent had a basal metabolic rate below minus 10 per cent (AM. J. OBST. & GYNEC. 30: 570, 1935). This group had both iodine and thyroid medication during pregnancy, but I do not have data to show whether or not any of them de-

veloped evidence of toxemia. However, I am convinced that women who have hypothyroidism are more likely to develop toxemia than normal women, and that with proper medication this possibility may be greatly reduced if not entirely eliminated. For several years I have urged routine determination of the basal metabolism as a part of prenatal care. Adequate treatment with iodine and thyroid medication during pregnancy is the most satisfactory way to meet the thyroid problem, as it greatly reduces the possibility of an abnormal thyroid in the newborn.

DR. JAMES E. DAVIS, ANN ARBOR, MICH.—Krogh, of Copenhagen, some years ago wrote a splendid monograph calling attention to the blood depots of circulation. He pointed out that 45 per cent of the body's blood was at rest under ordinary conditions and that only 55 per cent of the total mass of blood was in circulation. Under conditions that are depressive the depot blood is increased and the metabolic processes in the smaller vessels of the circulatory mechanism are associated with toxicity. If one studies the smaller vessels, especially of the placenta and elsewhere in the body, he will see that primary changes will take place in the walls of the smaller vessels. Attention is called to the placenta being one of the depots most involved in the pathologic processes of this condition. Therefore, it does not seem wise to attach too much importance to the infarcts. There is no satisfactory explanation given that will go far in accounting for all infarcts.

DR. RICHARD PADDOCK, ST. LOUIS, MO.—Since it is not expedient for every one to do basal metabolic rates on all patients, a most valuable substitute is to watch the change in the patient's weight. When the weight of the patient begins to follow an abnormal course, then we are adequately forewarned, that some change in metabolism is impending.

The expression "infarction of the placenta" is a very loose term. It can be compared to the term "cancer of the uterus." It does not tell us exactly where the change takes place or what type of infarction is going on. Observations associating toxemia with changes in the placenta date back as far as antiquity. It was only after the advent of the microscope and the understanding of placental histology, and later placental pathology, that the different types of placental infarction were recognized. The changes in the placenta resulting in infarction are brought about by perhaps three or more different types of changes in the elements present in the placenta.

DR. EVAN SHUTE, LONDON, ONTARIO.—I feel that there is a very real reason to be apprehensive of hypothyroids in pregnancy. Now almost all hypothyroids have high blood estrins. We routinely do blood estrin tests on our pregnant patients when first seen. As you perhaps know, if you inject estrin into animals you will produce a thyroid hypoplasia. Similarly patients who are hypothyroid have difficulty in excreting estrin.

Perhaps vitamin E administered to such patients exerts its effect through the estrin balance in the body and the thyroid. It has been shown by Singer in England that wheat germ oil will produce some hyperplasia of a thyroid which has been previously hypoplastic. We have had quite an experience now in giving vitamin E in the form of wheat germ oil to patients showing incipient toxemia. The results are encouraging.

DR. J. W. KENNEDY, PHILADELPHIA, PA.—In studying the etiology of any special lesion, we must not overlook the help which may come from the study of the physiology and pathology of analogous lesions elsewhere. According to Dr. Colvin in toxemia of pregnancy we are dealing with an infarct and its absorption, causing toxemic effects.

Heyd has called our attention to deaths of unknown origin following surgery of the liver. In all major operations in abdominal surgery there must be some disposition of operative detritus and blood clots, and the liver is the organ which finally disposes of all protein material, as a part of its metabolic function.

May we assume a similarity in the chemical composition of such postoperative clots and that of placenta infarcts? Of course, there is a marked difference in the histopathologic picture seen in both the liver and kidney of patients who have died

from either late or early toxemia of pregnancy, and those suffering from liver deaths of unknown causes. If this static blood incident to either clot formation or infarct were subject to drainage, it is my opinion, toxemia would not result.

We are familiar with the sudden deaths from ectopic pregnancy where necropsy reveals an insufficient amount of intra-abdominal hemorrhage to have caused a fatal issue. It is of little satisfaction to any earnest consideration of a subject for us to dismiss so tragic a death by saying it is due to shock from free blood acting as a foreign body within the abdominal cavity and thus dismiss the harmful consequence in the way of toxemia from absorption of the intra-abdominal blood or clots.

We do know this, that from an extensive experience in vaginal hysterectomy clamp method, where drainage is most efficient and there is no concealed or confined blood clots for absorption, we never find from necropsy lesions of the kidney or liver typical of any kind of toxemia.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—I would like to call attention to the fact that the most common cause of a high basal metabolic rate is a nodular toxic goiter or adenoma of the thyroid, and that the toxic symptoms usually become manifest between the ages of 35 and 45 years. In a large percentage the thyrotoxic basis for the increased metabolism is not diagnosed, for many clinicians associate thyroid disease with a prominent goiter or the staring eyes of the much less common exophthalmic goiter, which usually reaches a recognizable toxic stage between the ages of 25 and 30 years. As pregnancy may activate a dormant adenoma of the thyroid we would expect such activation to be more common in the later years of a woman's fertility, the adenomatous years. As the adenoma may be so small or so far within the chest as not to be felt, I feel that a pregnant woman, toxic and with an excessively high basal metabolic rate should immediately receive iodine or an iodide by mouth or parenterally pending the establishment of the diagnosis.

DR. COLVIN (closing).—Regarding Dr. Kennedy's statement concerning the avoidance of large stumps in pelvic surgery, it does not seem possible that such pedicles of tissue could be the origin of a sufficient quantity of guanidine to cause liver damage, inasmuch as Harding and Fort have already shown that various tissues of the body contain approximately one-half the amount of arginine as found in placental tissue.

As to whether the infarcts are the cause or the effect of toxemia, we emphasize that, contrary to Young's belief, the infarction is on the fetal side of the placenta and is concerned with the etiology of toxemia rather than the result of toxemia. The isolated lesions, thrombosed villous vessels and open intervillous channels in acutely infarcted tissue, as seen microscopically, offer proof of this claim. If the infarct is looked upon as a result of toxemia, why should isolated areas become involved in infarction while the remainder of the placental tissue escapes damage?

We wish to stress the element of fetal trauma as an important factor in the production of placental infarcts. The unprotected fetal circulation on the placental surface is unique. As a rule the organ is situated in the uterus, adjacent to the podalic pole of the fetus, exposing its unprotected vessels to the trauma of movements of the fetal extremities. In normal vessels no damage is done, but in cholesterol damaged vessels the intima is more likely to be broken, followed by thrombosis, embolism, and infarction of the involved tissue.

Talbot has pointed out the deviations in basal metabolism among young women from a geographical standpoint. It is our belief that this deviation from normal, rather than inadequate prenatal care, is one of the factors responsible for the high incidence of toxemia of pregnancy throughout the southern United States.

CLINICAL SYNDROMES REFERABLE TO FAILURE OF OVULATION

With Special Reference to Certain Cases of Sterility and Functional Bleeding

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SO BRILLIANT have been the advances made in our knowledge of the physiology of the female reproductive cycle, and especially of its endocrinology, that we are likely to lose sight of the fact that these cyclical phenomena are of only ancillary importance, and that the central actor in the whole process is the egg itself. To put it another way, the cardinal function of the female genital apparatus is childbearing and not menstruation. As a matter of fact, the actual bleeding of menstruation has a negative significance, for its occurrence is in general indicative of failure of conception.

The chronologic relationship between ovulation and menstruation is now well established, at least in that we know that the egg is not extruded at the time of menstruation, as was once believed, but at some time in the interval, ordinarily about midway between periods, with individual variations as to the exact day. We are still in the dark, however, as regards the hormonal mechanism involved. It can be said, however, chiefly on the basis of studies by Hisaw and his collaborators,[2] that the essential hormones are the gonadotropic principles produced by the anterior lobe, the follicle first maturing under the influence of the follicle-ripening principle, and rupturing only if to this is added a small proportion of the luteinizing principle. With ovulation as with so many other endocrine phenomena we deal with a delicate quantitative balance between hormones, and the evidence indicates that this balance varies in different species and in different animals of the same species. It is not surprising that disturbances of this mechanism may occur, and that ovulation therefore may fail to take place. In such cases it seems that the follicle hormone alone is produced, but for some reason the luteinizing mechanism is not touched off. Whether or not this luteinizing defect is always due to insufficient maturation of the follicle, as some believe, is not certain, though this seems unlikely in view of the fact that the unruptured follicle may continue to grow and to produce excessive amounts of the estrogenic hormone. On the other hand, the evidence indicates quite clearly that luteinization cannot occur unless follicle maturation has advanced to a certain point.

If ovulation fails to occur, the growth of the follicle is sooner or later checked, as we believe, by the reverse inhibitory effect of the follicle

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22 to 24, 1938.

For lack of space, certain portions of this paper have been omitted.

hormone upon the anterior lobe. More recently the studies of Smith, Smith and Pincus[3] have seemed to suggest that in the explanation of either normal menstrual bleeding or that of the abnormal so-called functional variety, we must consider not only the factor of hormone withdrawal, but also that of changing ratios between the various forms of estrogen. The progesterone found after ovulation is apparently the chief determiner of this changing balance. In the normal cycle it brings about a conversion of estrone into the less active estriol, which therefore shows a relatively high level during the luteal phase of the cycle. On the other hand, a drop in estriol precedes the onset of menstruation, as might be expected because of the regression of corpus luteum function occurring at this time.

The fact that in certain animals, such as the rabbit, the act of coitus is the determiner of ovulation, has led to much discussion as to whether the exciting factor of the pituitary is of nervous or endocrine nature. The recent work of Brooks[4] would seem to indicate that in rabbits the former is the case, the nerve paths reaching the pituitary from the hypothalamus by way of the pituitary stalk. For example, after severance of the stalk 18 rabbits failed to ovulate even though they mated frequently. This question is of some importance in its human connotations in spite of the fact that there is as yet no evidence whatever to support the belief of Grosser and others that copulation may be the direct exciting cause of ovulation. It will be recalled that this is one of the objections which has been urged against the reliability of the Ogino-Knaus doctrine of a "safe period," and the theoretical possibility of at least a vestigial degree of participation of the nervous system even in the human ovulation cannot be denied.

The bleeding of anovulatory cycles may occur with just about the same rhythm as the more common ovulating cycle, and it may be normal in amount and duration. So far as the woman herself is concerned, menstruation may in other words be essentially normal in character and rhythm, even when ovulation is not occurring.

A rather sharp division of opinion has arisen as to whether or not the term menstruation can be properly applied to include periodic bleeding of this nonovulatory type. There are many who insist that only when periodic physiologic uterine bleeding is associated with ovulation and corpus luteum formation, and when the actual bleeding is preceded by characteristic predecidual secretory changes in the endometrium should the term menstruation be employed. It is probably futile to belabor such questions of definition, but to my mind the above definition is a totally unwarranted limitation of the term "menstruation," which has always referred to periodic physiologic uterine bleeding regardless of its hormonal mechanism. For that matter, the term was employed centuries before we had the slightest conception of its mechanism, long before hormones were thought of, and long before ovulation was known to be in any way related to menstruation. In those early days, menstruation was thought of simply as a periodic purging of the woman's blood, the purpose of which was to rid her of supposedly unclean and noxious principles. It is in this sense that the word "menstruous" is

used some seven times in the Bible. Why should a term of such ancient vintage now be restricted to one particular hormonal type, even granting that this is by far the most common? One might almost as well argue that the term childbirth should be applied only when the baby is born by the common vertex mechanism, but not when an unusual or abnormal mechanism is involved, as with a breech or face presentation.

To emphasize how menstruation and ovulation, which most characteristically proceed hand in hand, may in a minority of cases diverge, let us review briefly the development of the menstrual function in the individual woman. On the basis of both histologic and hormonal studies it is known that a certain degree of follicle maturation and estrogenic

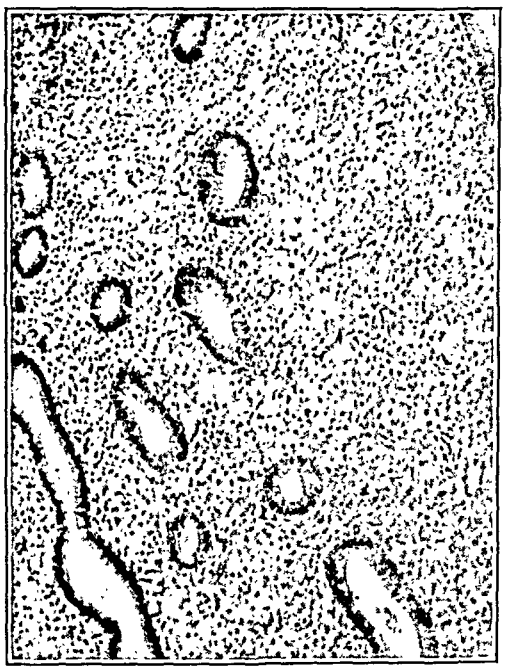


Fig. 1.

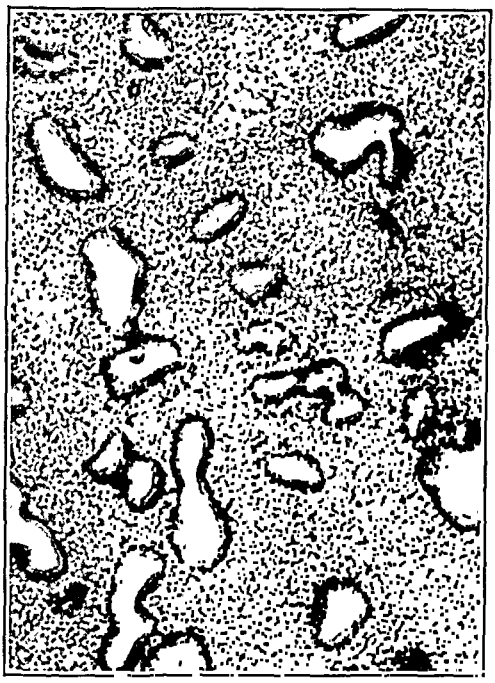


Fig. 2.

Fig. 1.—Endometrium obtained by premenstrual biopsy in a girl of 17 years. There is no suggestion of secretory activity, and it may be assumed that ovulation has not occurred.

Fig. 2.—Similar endometrium, also obtained by premenstrual biopsy, in a girl of 14 years.

function begins a considerable time, often several years, before the appearance of the first menstrual period. When estrogenic function reaches a sufficiently high point, the reciprocal influence upon the anterior pituitary brings about periods of regression associated with periodic bleeding, often with no follicular rupture or corpus luteum formation.

This is not a mere speculation, for it is readily demonstrable by the histologic study of the endometrium in young girls. Menstruation in such cases may be more or less irregular for many months, but not infrequently it is of approximately four weeks' type, with a flow which in amount and duration is within normal limits. Opportunities for studying the endometrium in cases of this essentially normal variety are for obvious reasons not numerous, but I have encountered a suf-

ficient number to convince myself that essentially normal menstruation may occur from an endometrium of almost any histologic type. Recently I have performed premenstrual endometrial biopsies upon a group of 6 young patients upon whom some type of surgical procedure was necessary. These patients were of the following ages: 14, 15, 16 (2), 17 (2). In only one of these, a girl of 16, was the typical secretory endometrial picture exhibited, the others showing various degrees of proliferative but non-secretory activity (see Figs. 1 and 2).

Such a small group of patients is of no value in indicating the actual incidence of nonovulatory cycles in the early period of menstrual life, but it does definitely establish the occurrence of such cycles in girls who to all intents and purposes are menstruating normally. I believe that when such observations are multiplied they will reveal that in young patients anovulatory cycles are very common, just as has been shown to be the case in immature monkeys. Moreover, such studies will quite certainly bear out the recent observations of Hisaw and his collaborators, as well as those which many of us have made on our human material, that bleeding can occur from almost any histologic type of endometrium.

Circumstantial evidence along this line is to be found in the studies of Mikulicz and Knausch[5] upon young primigravidas in the Berlin Frauenklinik. These indicate that a considerable number of such young patients, though leading active and unprotected sex lives, failed to conceive for a considerable time, often several years, after the menarche. Such studies are perhaps of limited scientific value, but they are strongly suggestive, in view of the definitely established occurrence of nonovulatory cycles in many young girls.

On the other hand, there is no doubt that in many, and probably the great majority, of girls, ovulation occurs from the first menstrual cycle, and that the very first menstrual bleeding is preceded by a first ovulation. That this must be true is indicated by the occasional occurrence of pregnancy before the appearance of menstruation. Furthermore, the fact is further established by the finding of secretory endometrium in premenstrual biopsy in many young patients. It is futile at the present time to talk of the numerical frequency of ovulatory as compared with anovulatory cycles at this phase of life, or for that matter, at any other phase. The simple fact is that a sufficient amount of accurate data is not yet available in the literature to justify any estimates on this point. It does seem clear, however, that either ovulatory or anovulatory cycles may occur during early menstrual life, and that in any one patient some cycles may be ovulatory and some anovulatory.

Why do some girls ovulate and others not? The answer to this question would at once convey the answer to the query as to what causes ovulation. The riddle is still locked up in the anterior pituitary, though definite progress has been made toward its solution. It seems to have been definitely established that rupture of the follicle alone is not sufficient to ensure luteinization, which can occur only if the follicle ripening process has advanced to a sufficient level.

The factors determining the release from the pituitary of the luteinizing fraction which seems to be indispensable for ovulation are not clear. As I have already mentioned, a sufficient degree of priming with the follicle ripening hormone is apparently not the only essential factor, in view of the failure of ovulation in the most common type of functional bleeding, that in which the follicle persists unruptured though functionally overactive. And yet, as we shall see, the use of anterior pituitary-like principles especially rich in the follicle-ripening principles has been suggested to induce ovulation in nonovulating women. Various theories as to the interplay between the pituitary and ovarian sex hormones have been suggested, but as yet the exact motivating force behind ovulation is a mystery.

As we approach the end of menstrual life, divergence of menstruation and ovulation is again frequently noted, and on this point it is possible to secure definite evidence by the simple method of premenstrual endometrial biopsy, as I have discussed in several previous papers.[6] Here again it is impossible to speak of the numerical incidence of anovulatory cycles, though the now numerous reports on this subject leave no doubt as to their comparative frequency. It is now fully justified to say that while probably the great majority of women ovulate until the end of menstrual life, and sometimes beyond, there are not a few in whom the cycle becomes anovulatory for a variable time before its cessation. It also is true that in many women some cycles are ovulatory, and some nonovulatory, a fact which must be remembered in evaluating the results of any method of treatment aiming to induce ovulation.

Between the two extremes of menstrual life, and therefore during the greater portion of reproductive life, there can be no doubt that the overwhelming majority of cycles are of the characteristic ovulatory type, but even here one finds not infrequent exceptions. It is only when these are intensively searched for that they are revealed, and the stimulus for such a search is commonly the effort to find an explanation for the cause of sterility in cases in which all other factors are apparently eliminable. I have thus far studiously abjured statistics in this discussion, for the study of anovulatory cycles in women at any age has been based chiefly upon the study of that small proportion of women who have been subjected to intensive study because of sterility of obscure causation. Such studies cannot give a true picture of the incidence of this type of cycle among women in general. Even in our sterility cases, only a small subdivision call for studies along this line, for in the great majority some other and perhaps very obvious cause is revealed, such, for example, as deficiency in the male partner, tubal closure, or definite endocrinopathies, to mention only the most important.

In my own private practice I have encountered, during the past three years, 39 cases of sterility of this obscure type, among a total of 142 of all types, in which all the more common factors could apparently be eliminated. This high proportion is to be explained by the fact that a great many of these patients had been previously studied elsewhere, and the more obvious factors, such as male sterility and tubal nonpatency, eliminated. In 19 of the 39 cases endometrial biopsy performed within

a few days before menstruation revealed a non-secretory type of endometrium, showing degrees of proliferative activity varying between pictures corresponding to an early interval phase at one extreme, to a marked Swiss-cheese type of hyperplasia at the other. Some of these patterns are illustrated in Figs. 3 and 4. Some degree of endometrial hyperplasia is the most common picture encountered, being found in 11 of the cases. In all of these cases menstruation was normal or approximately normal, though some showed a tendency to irregular tempo, and in some the menstrual amount was above the average, though not pathologic in the clinical sense.

The ages of these patients varied between 22 and 43. Of 10 patients between 20 and 25 years old 4 showed nonovulatory cycles; the same finding was noted in 4 of 11 between 25 and 30; in 3 of 7 between 30

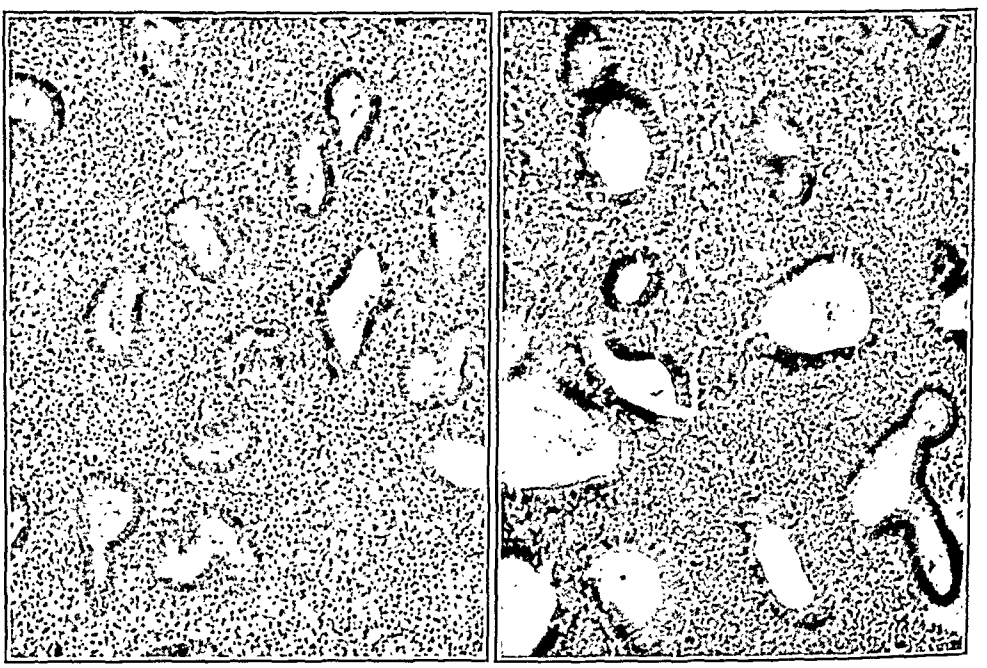


Fig. 3. Fig. 4.

Fig. 3.—Non-secretory premenstrual endometrium in a normally menstruating woman of 39 years. Biopsy three days before expected period.

Fig. 4.—Anovulatory type of premenstrual endometrium in a patient of 40 years. Biopsy day before expected period.

and 35; in 4 of 6 between 35 and 40; and in 4 of 5 between 40 and 45. One thus gets the impression that failure of ovulation is to be borne in mind as a possible cause of sterility, especially in women who are approaching middle life, though it may occur at any age. Sterility in women at a late phase of menstrual life is not by any means an infrequent problem, not only because of the frequency of late marriages, but also because in voluntarily one-child marriages another child is wished for before the menopause, not infrequently because of the death of the first. A number of patients of this type are included in the group mentioned above.

It is not often practical, nor is it usually advisable in the case of women anxious to conceive, to perform endometrial biopsy repeatedly,

because of the great danger of destroying the patient's chances for the particular cycle, should an ovum have been given off and been fertilized. However, from the study of a number of patients on whom I have had opportunity to make such biopsies at intervals, I believe there are some who ovulate with some cycles and not with others, but that more frequently ovulation is likely to be completely in abeyance for considerable periods of time, just as it is in the case of the common type of functional bleeding. The fact that nonovulation may be a sporadic occurrence, however, should make us very conservative in the evaluation of therapeutic measures for this condition.

Even when absence of ovulation is established as the probable cause of sterility, not a great deal can as yet be offered to the patient by way of correcting the defect. Our ignorance of the exact hormonal factors concerned in ovulation explains our present-day floundering in this particular field of organotherapy, as in so many others. Patients of this group characteristically exhibit no other evidences of endocrinopathy, and are usually in good general health. In spite of this, small doses of thyroid are commonly used on more or less empiric grounds. In an effort to induce ovulation, various methods have been used. Among these has been the administration of pregnancy urine preparations, in the hope that, as in the rabbit, these might bring about rupture of the follicles, a hope which has not been fulfilled. This is not surprising in view of the notorious species differences exhibited in this as in other endocrine processes. Only Büttner[7] seems to have noted any histologic effect upon the endometrium from the use of pregnancy urine preparations, combined in some cases with transfused pregnancy blood, reporting secretory changes in a considerable proportion (12 of 16), an observation not supported by others. The administration of a single large dose of estrogenic hormone is believed by some to promote ovulation.

More recently a good many clinics have been experimenting with the use of the gonadotropic principles found in the blood serum of pregnant mares in high concentration at a certain phase of pregnancy, and especially rich in the follicle ripening hormone, as first demonstrated by Cole and Hart[8] in 1930. There is considerable evidence that in such animals as sheep and sows, ovulation is stimulated by this principle and fecundity increased. As yet, however, we know very little as to the effects upon the human ovary, which may respond very differently, if one may judge from the wide species differences in the ovarian response to most other gonadotropic substances.

A very recent publication of Davis and Koff[9] represents a praiseworthy effort to study the problem in human patients, though the results can as yet be considered only suggestive. There are two obvious criticisms of this study as bearing on the possible artificial induction of human ovulation. As the authors themselves say, the majority of their patients were probably having normal ovulatory cycles, so that one would certainly hesitate in ascribing ovulation to the mare serum gonadotropic hormone which was injected intravenously. The results therefore are far less impressive than if a group of patients had been available in whom the nonovulatory type of cycle could be assumed or demon-

strated, as for example, cases of periodic functional hemorrhage associated with a non-secretory type of endometrium. It is of interest to note that 3 of the 36 cases studied by Davis and Koff were actually of this type, and in none of these was any evidence of ovulation found after the gonadotropic injections.

Equally cogent is the objection that must be faced by the authors in their interpretation of the age of the corpora lutea found in the ovaries of their patients, and in their concept of what constitutes evidence of recent ovulation. It is hazardous to base opinions on reproduced photomicrographs, but there will certainly be no general agreement as to the histologic interpretations of the illustrations offered by the authors as evidences of recent ovulation. For example, their Fig. 2, labeled as "showing the general characteristics of a freshly ruptured follicle" and depicting a large corpus, with well-developed antrum partly filled with blood, and with what is apparently a well-formed convoluted lutein zone, would impress many as representing a corpus a good many days old, certainly much older than the period elapsing between injection and operation. Similar comments could be made on other illustrations, my only reason in mentioning this being to stress the uncertainties of conjectures as to the age of corpora lutea on the basis of gross and to some extent also of the histologic pictures.

There are now many "physiologic-minded" gynecologists who have accustomed themselves to careful inspection of the ovaries at operation, in correlation with the cyclical chronology of the patient. There are few, however, who would feel sure of themselves in recognizing mature follicles, which, in my experience, are much less conspicuous than many atretic follicles. The latter, indeed, are more likely to present prominently on the ovarian surface than mature follicles. Likewise, a very early corpus luteum is commonly entirely beneath the surface of the ovary, as the study of histologic sections reveals. Its wall is characteristically crumpled and collapsed, the lumen often being a convoluted slit, though at times more open. In its earliest stages its wall is about as difficult to distinguish from the wall of an unruptured mature follicle as is the predecidual endometrium of the nonpregnant woman from the earliest stages of genuine decidua. Meyer[10] and many others, including myself,[11] have described the characteristics of very early corpora, and the subject calls for no further elaboration here.

It is quite certain that within the next few years we shall have available much more information as to the effect of the gonadotropic substances of mare serum upon both the ovulating and nonovulating human cycles, and as to whether or not it is to be of value in promoting ovulation in the latter group of patients. Certainly the problem calls for investigation, in view of our lack of other effective measures for this condition. The fact that in many non-ovulating cases we are dealing with what we believe to be an already existing relative excess of the follicle ripening hormone is confusing, but need not necessarily inhibit our efforts to determine the effects of administering principles which are so dominantly follicle-ripening as are the mare serum preparations.

In actual practice one must base one's impressions of the value or lack of value of this form of treatment upon other methods than inspection of the ovaries. The occurrence of pregnancy in previously nonovulating patients would be of some value if it were observed with any degree of consistency following such treatment, but there is no evidence whatever on this point as yet. The demonstration of ovulation by endometrial biopsy, in previously nonovulating patients, would likewise have some value, though it could not be considered convincing, for reasons already indicated. Most valuable as evidence would be the production of ovulation and normal menstruation in the group of cases in which failure of ovulation for long periods of time is so characteristic, viz., the functional bleeding cases. Here again we have no evidence of accomplishments as yet.

Finally, attention must be called to the valuable new approach made available through the work of Venning and Browne,[12] who have shown that a reliable index of progesterone activity is obtained through the demonstration of pregnandiol in the urine. That the latter is an excretion product of the corpus luteum hormone now seems well established, and it seems certain that increasing use will be made of this method in the study of cases of endocrinopathic sterility, as well as in those of habitual abortion.

The other important clinical syndrome due to failure of ovulation is the common type of functional uterine bleeding. As a matter of fact this type of bleeding is invariably characterized by sterility, because of this very absence of ovulation. There are other less common varieties of functional bleeding to which this statement would not necessarily apply, such as those due to quantitative deficiency of progesterone, those due to functional deficiency of the uterine musculature, and those attributable to disorders of the vascular apparatus or vasomotor nerves. The most frequent variety, however, is that due to failure of ovulation, with functional persistence of the unruptured follicle for a variable time, and a consequent persistence and excess of estrogenic influence, associated with absence of progesterone.

In this field, as well as in that of endocrinopathic sterility, studies on the pregnandiol content of the urine should prove increasingly useful in separating cases of functional bleeding into those due to failure of ovulation and those due to other factors. The few data as yet available on this point confirm existing impressions as to the common failure of ovulation in these cases, and fortify our reliance upon microscopic examination of the uterine mucosa in the classification of our cases.

The characteristics of the endometrium found in cases of functional bleeding have been described in my previous papers.[13] It is always non-secretory, most frequently exhibits some degree of hyperplasia, but may be of the normal interval type or even atrophic. Hyperplasia of the endometrium is certainly not to be looked upon as a cause of bleeding, for it represents only an exaggerated growth effect produced by estrogen upon the endometrium. The bleeding phases are, in the light of our present knowledge, to be looked upon as due to drops in estrogen level dependent upon the shuttle-cock interplay between the anterior

pituitary and ovarian sex hormones, and possibly also to the changed proportions between estrone and estriol entailed by absence of progesterone, as already discussed.

This is not the place to discuss the clinical aspects of functional bleeding, nor the details of its treatment. In many patients, particularly those in the younger group, there is a definite place for organotherapy. A number of methods have been used with varying success. It is of interest to note that none of these have in the past been directed toward correction of the fundamental abnormality, which is a failure of ovulation dependent upon pituitary dysfunction. First may be mentioned the use of the prolan containing pregnancy urine principles, as suggested by Novak and Hurd[14] in 1931. In our very first paper we pointed out that any beneficial effect of such treatment was not due to a production of luteinization in the ovaries, similar to that produced by prolan in the ovaries of such experimental animals as mice or rats. The fact that the human ovary does not respond in this way has since then been abundantly confirmed not only in our own clinic but also by the studies of Hamblen and Ross,[15] Hamblen and Thomas,[16] Geist[17] and others. The evidence seems conclusive that the pregnancy urine principles never produce follicle stimulation in the human ovary, and that they are not capable of bringing about the extensive luteinization seen in the ovaries of some animals. We are still ignorant of the mechanism of the good results obtained in at least a considerable proportion of cases of functional bleeding from the administration of the anterior pituitary-like substances of pregnancy urine. For that matter we are still in the dark as regards the nature of the relationship which undoubtedly exists between the chorionic hormones and the pituitary sex hormones themselves.

Since corpora lutea are characteristically lacking in the group of functional bleeding cases now under discussion, it is natural that progesterone should have been resorted to in the matter of treatment, now that active preparations of the latter are readily available. My own experience has led me to the belief that the pregnancy urine preparations are more frequently helpful than those of progesterone, and that there is perhaps some principle in pregnancy urine more frequently hemostatic than the hormone progesterone itself.

The most recent organotherapeutic trend in the management of functional bleeding has been in the administration of certain male hormone principles, particularly testosterone propionate. The past year or two has shown an amazing wakening of interest in the study of the effect of androgenic substances upon the female organism, and the literature of the subject is growing by leaps and bounds. While not directly touching on our immediate subject, the effects of androgenic principles in bringing about alteration of sex characters in female animals have been of special interest. Greene and Ivy,[18] for example, were able, by the injection of large amounts of androgenic substance into pregnant rats, to bring about permanent masculinization of genetically female offspring. Such animals exhibited the development of a penis. Cow-

per's glands, and a prostate, while all except the lower portion of the vagina was absent. Even the gonads showed a definite histologic trend toward masculinization.

As more pertinent to our present discussion may be mentioned that various authors have demonstrated the inhibitory effect of androgenic hormone, commonly in the form of testosterone propionate, upon the estrous cycle of rats (Ihrke and D'Amour,[19] Browman[20]), mice (Robson[21]) and monkeys (Zuckerman[22]). More recently Gaines, Salmon and Geist[23] have shown by biopsy studies of normally menstruating women after treatment with testosterone propionate, that there is a disappearance of the secretory phase in the endometrium, with inhibition of the proliferative changes, so that the endometrium may become hypoplastic or atrophic. It seems logical to believe that these effects are brought about, as these authors suggest, through the medium of pituitary inhibition by the male hormone rather than through a direct inhibitory effect upon the ovary or a peripheral effect upon the endometrium, as others have suggested. A similar inhibitory effect upon the vaginal mucosa has been recently described by Schorr, Papanicalaou and Stimmel.[24]

It is not surprising, therefore, that many of us have felt that the now readily available commercial preparations of testosterone might be useful in cases of functional uterine bleeding, in which we often seem to be dealing with a hyperestrous phenomenon. A number of favorable reports have already appeared (Loeser,[25] Geist and others[26]). My own experience, as yet not large, has led me to believe that this plan constitutes a valuable addition to our armamentarium in the treatment of the many cases in which more effective measures are undesirable, chiefly because of the patient's age and the desire for future reproductiveness. The method is much too new to permit of intelligent evaluation, or statistical comparison with other methods of organo-therapy.

SUMMARY

Concerning many of the endocrinologic matters upon which I have merely touched, an enormous literature has developed, but this I have refrained from reviewing in this brief summarizing paper. My purpose has been simply to call attention to the fact that failure of ovulation occurs not infrequently in ostensibly normal women, and that it is the responsible factor in at least a small proportion of sterility cases and in the most frequent variety of functional bleeding.

With reference to the former problem there is after all much analogy between the two sexes. The more cases of sterility I see the more I am impressed with the frequency and importance of the male factor. Complete aspermia is not at all infrequent in men who otherwise seem quite normal, and in whom there is no history of gonorrhea, mumps, or other infections, and in whom the genitourinary specialist finds no evidence of infection of the prostate or seminal vesicles. The same statement can be made as to necrospermia, which likewise is a frequent finding. That such cases, like our anovulatory cases in women, or like those in which defective ova lead to early and perhaps repeated abortion, are of endocrine causation, probably of pituitary source, seems certain. It is important to recognize these abnormalities of ovulation, even though we must await further developments before we can hope to treat them with any hope of consistent success.

The same fundamental defect, a failure of ovulation, is concerned in the most common variety of functional bleeding, and likewise implies a primarily pituitary dysfunction. If we could therapeutically bring about ovulation in such cases, we would be attacking the problem at its source. Instead of this, we must for the present depend on more superficial methods, such as the use of the anterior pituitary-like pregnancy urine principles, progesterone, and the androgenic hormone. A promising field of investigation in the effort to find a means of promoting ovulation in nonovulating women is the study of the effects upon the ovaries of ovulating and nonovulating women of the gonadotropic principles found in the blood serum of pregnant mares.

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DISCUSSION

DR. ROBERT A. ROSS, Durham, N. C.—Dr. Novak's study in the young female recalls the fact that bleeding can occur from any type of endometrium. As a matter of fact Hamblen from our clinic has reported a case of fatal uterine bleeding in a 17-year-old colored girl and the endometrium was atrophic.

Frequent reference to endometrial biopsy material has been made. We find the biopsy forceps indispensable. To give exact information the biopsy should be taken within the first twelve hours of bleeding, and the findings be interpreted as the sum total result of endometriotropic response. It does not allow a segregation of individual factors.

For the past year Hamblen has been making estimates of pregnandiol from a variety of patients. Perusal of his unpublished data is full of information and full of surprises. The appearance of this product in the urine is dependent on several factors. Progesterone is formed by corpora lutea after ovulation, with a definite possibility of its being formed by the luteinized marginal granulosal cells in follicles. (Such changes have been described in previous studies.) The removal of ovaries containing healthy lutein cells results in disappearance of pregnandiol from the urine. The endometrium aids in the alteration of progesterone into pregnandiol and its removal by curettement or hysterectomy results in cessation of excretion. The liver helps in the conjugation of pregnandiol with glucuronic acid and the kidneys excrete sodium pregnandiol glucuronide. When we consider the variables of production, elaboration, utilization, metabolism, and excretion, we see pos-

sibilities of deviation. We also see the need of a method whereby the levels of progesterone or its products in the blood can be estimated. Variations occur in the excretion of this product in women thought to have normal menstrual cycles and the relationship to the onset of menstruation is irregular. The excretion is not continuous throughout the progestation cycle. Immature or markedly hypoplastic endometrium may not be capable of metabolizing progesterone, and it seems reasonable that progesterone must be altered before it can aid in progestational differentiation. This explains the feasibility of sensitizing atrophic endometrium before the use of the active principle of corpus luteum if a progestational reaction is to be obtained. The ability of the endometrium to metabolize intrinsic and injected progesterone may differ.

Even after the progesterone is metabolized there is no assurance that every endometrium will utilize the product for progestational proliferation. The appearance of the pregnandiol complex in the urine may occur without an associated progestational endometrium. Hamblen ascribes these paradoxes in part to a lowered sensitivity or refractivity of the endometrium and leads to the conclusion that the excretion of sodium pregnandiol glucuronide may not be evidence that an endometrium is undergoing progestational proliferation, nor a failure of its excretion that ovarian function is inadequate. Thus bleeding from an estrogenic endometrium may not be "anovulatory" in character. Thus biopsy, pregnandiol determination and possibly the electric potentiometer are all necessary before the diagnosis of this condition can be made.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—An inheritance factor as a cause of sterility may exist as a recessive characteristic. In connection with that I would like to call your attention to some experiments on animals. The heterozygotic type of crested canaries and a breed of orange yellow mice, studied by Cueno, carries a so-called lethal gene. This is shown by the fact that among the young of those animals there always dies soon after impregnation of the ovum, the homozygotic, crested or yellow, type. There is a theoretical possibility that this may be true in human beings also. Perhaps in those cases where we see a prolongation of the menstrual cycle, it was really a very early abortion.

DR. NOVAK (closing).—Functional bleeding must be considered essentially as a disorder of ovulation. It seems reasonable to believe that when we know more about the hormonal mechanism of ovulation in the human being, and how to induce ovulation in nonovulating women, we shall likewise have a far more direct and successful method of treating functional bleeding than the more superficial and often unsuccessful endocrine methods now available, through the administration of preparations containing testosterone, progesterone, or prolan.

As regards the value or lack of value of pregnant mare serum in inducing ovulation, I may say that this problem has been extensively studied in monkeys by Dr. Carl Hartman, of the Carnegie Institute of Embryology, who has not as yet published his results, but who has permitted me to quote them here. Monkeys are certainly the ideal animals for experimental study, for they menstruate just as do women, and, like the latter, not infrequently menstruate without ovulating. Moreover, it is far easier to determine the occurrence of anovulatory cycles in monkeys than in the human being, for this can be readily and accurately done by rectal palpation, as Dr. Hartman has shown. In a series of 104 nonovulating monkeys in which pregnant mare serum was injected intravenously in various and often large or repeated dosage, Dr. Hartman noted ovulation in only 7. Even in these I suppose it is difficult to eliminate altogether the ever-present possibility of spontaneous ovulation. These results are anything but impressive, and since no such criticism could be made of the method of study employed in this series as I have made of the study of Davis and Koff, I believe that we may conclude that the value of pregnant mare serum in inducing ovulation still remains to be proved.

THE ETIOLOGY OF OCCIPUT PRESENTATIONS*

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(From the Department of Obstetrics and Gynecology, University of Kansas)

SEVERAL years ago we became interested in the management of occiput posterior and attempted a review of our experience, but soon found that our diagnoses of presentation were frequently unreliable in several respects. Many of the diagnoses had been made by interns and had not been checked by more experienced observers. In several instances, particularly in private patients, the attendant had arrived rather late and, because external rotation was toward the left, had decided that the presentation must have been O.L.A. The younger men, frequently, did not consider the possibility of an occiput posterior, even when, by abdominal examination, the findings pointed strongly in that direction. It very soon became apparent that a much better method of diagnosis, carefully controlled by experienced examiners, would be necessary before any accurate idea of the incidence of the various positions could be developed. Most of the textbooks in the more recent editions had included a statement that occiput posterior was probably more frequent than had been generally supposed. These texts had, in fact, revised their estimates upward from a very small percentage in earlier editions to as much as 25 per cent in the more recent.

In order to arrive at as accurate an idea of the incidence of the various positions as we possibly could, we set up the following plan: (1) That diagnoses of presentation and position should be made as early in labor as possible; (2) that at least two examiners should check one another; (3) that the diagnoses of the intern should not be accepted in any case; and (4) that if the labor had progressed to complete dilatation and the head had descended nearly to the pelvic floor, no diagnosis at all (beyond unclassified cephalic presentation) would be made.

We have tried to follow this plan carefully ever since and we believe we have a more accurate idea of the frequency of the various positions than before. We have not, of course, been able entirely to eliminate errors in diagnosis, but would estimate that the gross error in our present figures is probably not greater than 5 per cent. It should be noted that of the total of 2,282 cases, here reported, 109 are diagnosed under the term "cephalic." This includes patients seen late in labor and those upon whom the diagnosis has not been definitely made, either because of a very large caput or paucity of examinations due to eclampsia or some other inhibiting condition. Several of these patients were thought to have had occipitoposterior presentation, but the diagnosis was not clearly established.

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22 to 24, 1938.

One hundred seventy-one patients had diagnoses of brow, face, bregma, shoulder, breech or twins, and hence were excluded from this discussion of occiput presentation of a single fetus in utero.

This leaves a total of 2,002 occiput presentations where the diagnosis was carefully made and considered reliable for classification according to position. In each instance, the direction of the sagittal suture and the position of the posterior fontanel have been recorded on the chart early in labor. In the vast majority of these cases, this record has been made previous to 6 cm. dilatation. We have labeled as occiput anterior all cases where the sagittal suture was anterior to, or exactly in, the transverse, but never posterior to that point, and have designated as posterior only those instances where the small fontanel was actually back of the transverse diameter of the pelvis.

Since using this method of diagnosis and plan of classification of position, we have had 863 O.L.A. patients; 649 O.D.P.; 332 O.L.P.; and 158 O.D.A. (total: 2,002 patients). These figures are, in some respects, in quite sharp contrast with even our present ideas of the incidence of the various positions. O.D.A. is, in this series, the least common, instead of the usually quoted O.L.P. Presentation in the left oblique diameter (O.L.P. and O.D.A.) is less common than in the right oblique, as usually stated in the various textbooks. On the basis of these revised figures, it occurred to us that perhaps a more adequate explanation of the etiology of position might be made available.

If no factors other than pure chance were at work, presentation should occur with equal frequency in each of the four quadrants of the mother's pelvis. That other factors are at work has been agreed to by most authors, although some of the explanations offered have not been entirely acceptable.

Beck[1] states that "the smooth, dorsum of the fetal ovoid better fits the anterior wall of the uterus which lies in contact with the abdominal wall." DeLee[2] observes "with the woman in the erect position, the back of the child will naturally occupy the roomy anterior half of the uterus." Schumann[3] says, "with the mother in the erect position and moving about, the fetal back naturally tends to occupy the roomy anterior portion of the uterine cavity, especially if the abdominal walls be slightly relaxed." None of these sound very convincing. On the other hand, Beck[1] says, "the presence of the rectum on the left side tends to make the left oblique diameter somewhat shorter than the right," and Williams (Stander)[4] says, "the occiput is usually found at one or the other extremity of the right oblique diameter of the pelvis, owing to the fact that the left oblique diameter is materially encroached upon at its posterior extremity by the rectum" and Kerr and Ferguson[5] "the left oblique diameter is occupied at its posterior end by the pelvic colon which appreciably diminishes its total space," all of which sound much more plausible.

None of these authors mention the fact that the urinary bladder is, in part, a pelvic organ and that it, when distended, frequently encroaches upon the right anterior aspect of the pelvic inlet. As a matter of fact, photography of the pelvic inlet at autopsy (Figs. 1 and 2) shows that the bladder, when containing as little as 75 c.c. of fluid, really takes up considerable space. No doubt, with the full-term pregnant uterus occupying its usual position in the pelvis, the bladder would be considerably more flattened from before backward than is shown in these

pictures. Nevertheless, the fact remains that it must, on occasion, act as a considerable hydrostatic wedge. We have concluded that what otherwise might have been an O.D.A. presentation is frequently changed to an O.L.A., or to an O.D.P. This rotation of the head from an O.D.A. presentation to one of the other two, would, it seems, occur more frequently toward the O.L.A. than toward the O.D.P., except in those instances when it had primarily come down with the occiput somewhere near the transverse on the right side.



Fig. 1.—Pelvic inlet with bladder empty.

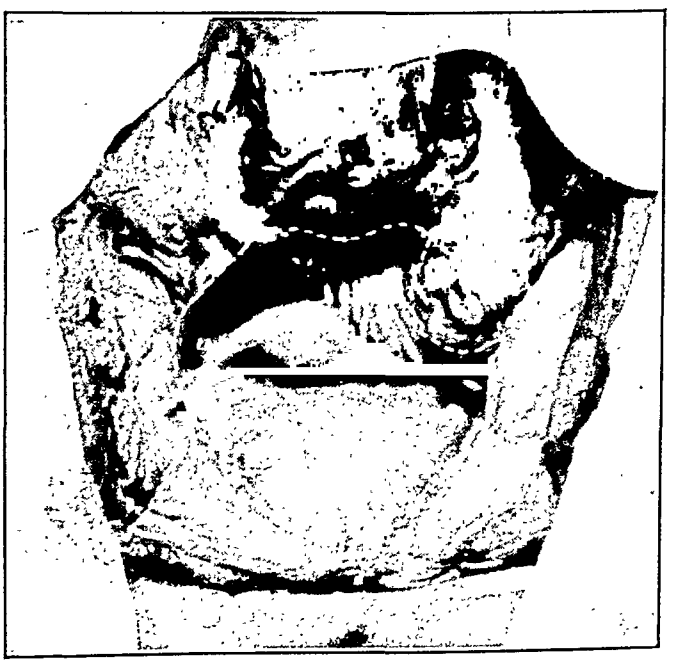


Fig. 2.—Pelvic inlet with 75 c.c. of fluid in bladder.

The pelvic colon, on the other hand, when distended, and thereby changing what was primarily an O.L.P. presentation into something else, would naturally in all cases produce an O.L.A., as it would be rather difficult to push the presenting part past the projecting promontory of the sacrum. We have actually observed one instance where the administration of a one pint enema to a patient early in labor caused rotation from an O.L.P. to an O.L.A.

The relative frequency of the four positions, as above indicated for this series, is quite suggestive when translated to the percentage basis, or to a measure by single digits. They are:

O.D.A.	8 per cent	1
O.L.P.	16 per cent	2
O.D.P.	32 per cent	4
O.L.A.	43 per cent	5+
Total	99 per cent	12+

Pure chance on this basis would cause each position to occur three times in the total of 12 plus. It would seem, on the basis of these two thousand cases that something prevented the occurrence of O.L.P. in one-third of the cases (slightly more often in multiparas and slightly less often in primiparas) and that perhaps all of this one-third had been added to the O.L.A. group. Likewise, one might conclude that some factor may have prevented the occurrence of O.D.A. in two-thirds of the instances where it would have occurred if only governed by pure chance, and that this factor had shifted the position to O.D.P. about one-half the time and to O.L.A. the other half. On this basis, the urinary bladder would seem to be twice as great a prohibitive factor as the pelvic colon against presentation in the left oblique diameter.

SUMMARY

If presentation in the right oblique diameter occurs with much greater frequency than in the left oblique, as is generally agreed by most writers (about seven to one) and has occurred roughly three to one in this series, it would seem that some more adequate explanation than the presence of the pelvic colon in the left posterior quadrant of the pelvis must be offered. The presence of the urinary bladder in the right anterior quadrant convincingly offers this additional explanation and, in fact, the bladder would seem to be a more important factor than the pelvic colon.

It may also be noted that the total of occipitoposterior presentations (981) approximates the total of occipitoanterior presentations (1,021). Possibly, therefore, occiput posterior is not such a serious complication as we have been urged to believe. We hope to discuss this subject soon.

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DISCUSSION

DR. F. J. SCHOENECK, SYRACUSE, N. Y.—We have been interested in this subject at the Syracuse Memorial Hospital because of the growing impression that posterior positions are far more common than ordinarily stated in the textbooks. In this connection I would like to ask Dr. Calkins his reason for including L.O.T. and R.O.T. positions as essentially anterior. These particular positions are usually considered as essentially posterior, especially as far as mechanism is concerned.

In presenting our figures from Memorial Hospital, I must admit that the series is not as carefully controlled as is that of Dr. Calkins. The cases do come, however, from a teaching service and in general have been checked rather systematically. There were 3,999 vaginal deliveries from 1934 to 1937; of these 3,585 are used for the statistics as being the usual vertex presentations.

Using Dr. Calkins' method of including transverse cephalic positions in the anterior group, our percentages are, L.O.A., 44 per cent; R.O.A., 26 per cent; R.O.P., 20 per cent; and L.O.P., 10 per cent.

If we regard the transverse cephalic presentations as essentially posterior the percentages become: L.O.A., 39 per cent; R.O.P. and R.O.T., 24 per cent; R.O.A., 21 per cent; and L.O.P. and L.O.T., 16 per cent.

These figures confirmed our impression of a more frequent incidence of posterior positions in our institution than is ordinarily stated, namely 40 per cent.

That the distended bladder may become a factor in delaying descent and perhaps interfering with rotation is certainly an occasional observation. If the bladder can influence mechanism of labor, it would seem it might also be a factor in determining position.

DR. A. LOUIS DIPPEL, BALTIMORE, MD.—I am wondering what Dr. Calkins' impression is of the actual incidence of occiput transverse positions, which he has grouped with the occipitoanterior positions. Caldwell and Moloy, from an elaborate stereoroentgenologic study of a relatively small series, have shown the importance of transverse positions in the mechanism of engagement, for they have found that transverse positions far exceed those of the oblique positions, the head engaging in occiput transverse in 60 per cent of 200 cases. Plass, from a clinical study, found engagement of the fetal head taking place in the transverse positions in 21.8 per cent of 5,445 deliveries. In our own clinic, we find that engagement always occurs in a transverse position in the markedly contracted rachitic pelves. Furthermore, with the advent of the studies of pelvic architecture, it has become evident that engagement does occasionally take place with the head in direct occiput anterior or direct occiput posterior. Caldwell and Moloy report engagement occurring in direct occiput anterior in 5.5 per cent of 200 cases or 17.7 per cent of 59 cases of anthropoid pelves.

The pelvic colon and the urinary bladder must play some part in the mechanism of engagement. Dr. Calkins has cited the influence of a colon distended by an enema. Occasionally, a distended bladder is known to prevent engagement of the fetal head but with relief of the distention engagement occurs promptly. In the 1920 edition of his textbook, DeLee describes a case in which a distended bladder caused rotation of an originally obliquely anterior to an obliquely posterior position, but with drainage of the bladder the head returned to and engaged in the original occipitoanterior position. The bladder occurs as a right lower abdominal mass with almost the same frequency as dextrorotation of the uterus, statistics showing that this is the position of the uterus in 80 per cent of the cases and Williams stating that the bladder is pushed to the right by rotation of the uterus on its vertical axis in possibly 90 per cent of all pregnant women. If the hydrostatic wedge formed by the urinary bladder were of prime importance in the production of engagement of the fetal head in the right oblique diameter, then the combined percentages of L.O.A. and R.O.P. should approach these figures. This is the case in Dr. Calkins' series, yet he has included occipitotransverse with occipitoanterior positions.

From a stereoroentgenologic study of over 300 pelves, most of which were contracted in at least one diameter of the pelvic inlet, we have had to conclude that in contracted pelves the position of engagement is most often determined by the

shape and size of the pelvic inlet. Frequently, as in the cases of markedly contracted rachitic pelves, accommodation of the fetal head, on account of the marked shortening of the obstetric conjugate, can take place only with the occiput in the transverse position. In contracted pelves, then, we cannot ascribe to the hypothesis that the urinary bladder causes the fetal head to engage most often in one or the other position of the right oblique diameter of the inlet. However, where the pelvic inlet is large, so that accommodation does not have to take place and particularly where the pelvic inlet is circular in shape, the bladder may well act as a hydrostatic wedge to influence the mechanism of engagement.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—I agree with Dr. Calkins in general, though I wish to mention another point, that is the physiologic position of the uterus. The pregnant uterus physiologically is not in the midline but falls backward and to the right. Therefore, the left side of the uterus will be more forward. That makes it understandable that O.L.A. and O.D.P. are more frequent than O.L.P. and O.D.A. As the statistics show that O.L.A. is twice as common as O.D.P., therefore it is natural that O.D.A. is less frequent than O.L.P.

I believe that one who especially looks for occiput posterior cases will find them more frequently. But we know also that the majority of these cases show no delay of labor and therefore it has no great practical importance. In the cases where there is a delay we see a prolongation of the first stage and a tardy descent of the head into the pelvic cavity. For the tardy descent of the head I offered four years ago the following explanation:

It is well known that the anterior wall of the bony pelvis or os pubis is much lower than the posterior wall formed by the hollow of the sacrum. As the head traverses the pelvis in the direction of the so-called pelvic axis, all points of the presenting part do not advance an equal distance. The part nearer the pubic arch reaches the outlet sooner than that approaching the sacrum. The situation resembles the bend in a circular race course, where the competitor on the inner side has a shorter distance to travel. In the occipitoanterior positions the small fontanel is in the anterior part of the pelvis and after a descent of only a few centimeters reaches a point deep in the pelvis. On the contrary, if the small fontanel is in the posterior section of the pelvis, or occipitoposterior position, the head will not have engaged in the inlet after traversing the same distance. Obviously, if the small fontanel is in the posterior quadrant of the pelvis the course of labor will be more difficult. The difficulty will be relatively insignificant if uterine action is vigorous or if the head is small in comparison with the pelvic diameters.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I can understand the influence of the bladder and of the rectum in producing a posterior position, but there are other factors. Not only the pelvis but the abdomen may have something to do with the position, and the relaxation of the abdominal wall may be expected to have some effect on position. Last, it would seem to me that the site of the placenta would have a lot to do with position.

DR. CALKINS (closing).—I will try only to answer the questions of why we class the occipitotransverse positions as anterior. There was no attempt to do that. We were interested in a study of occiput posterior and were studiously avoiding the inclusion as an occiput posterior of any case which was, or might be interpreted as, an occiput anterior.

THE INCREASED INCIDENCE OF FETAL ABNORMALITIES IN CASES OF PLACENTA PREVIA*

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IN 1923[10] I wrote a paper in which I tried to point out the relationship between placenta previa and fetal monsters and deformities. Today I should like to present additional evidence that abnormal babies occur more often in cases of placenta previa than otherwise.

In discussing the etiology of monsters it has been customary to distinguish two types. First, the monsters in which the proper conditions to produce them are already in the germ (and are therefore inherited) and second, those deformities which are due to certain external influences which act upon a normal ovum after it is fertilized. In the first group belong such deformities as polydactyly, polymastia, cleft palate and others. Many monsters have been shown to depend on genes. A deformity such as hydrocephalus may be inherited in some individuals and it may be due to external factors in other cases. Furthermore, in some instances monsters may be due to a combination of hereditary and environmental factors. When there is an hereditary tendency to monsters, the environment may determine whether or not a monster will develop in a particular case. However, many embryologists believe that heredity plays only a small role in the etiology of monsters whereas changes in normal eggs brought about by a variety of factors are responsible for most monsters.

Ballantyne says, "There is good reason for believing that malformations and monstrosities are the product of morbid agents acting during the embryonic period." Mall says, "A more careful study of my specimens . . . establishes beyond doubt . . . that all of them (163 pathologic human embryos) are developed from normal ova due to external influences . . . to a condition which I shall term faulty implantation." Mall also says, "Hertwig concludes properly that every human ovum has within it the power to develop into a monster, either anencephalic or otherwise and that it is not due to any abnormal condition of the germ, but to external influences that affect the growth of the egg." Mall pointed out that His was inclined to abandon the theory of germinal origin of pathologic ova altogether. Giacomini, another student of pathologic embryology, emphasized the necessity for studying the form and structure of the decidua in normal as well as pathologic ova for at this point mechanical and nutritive influences must occur which are of prime importance in the production of early pathologic embryos. Likewise, O. Hertwig believed that the power to become monstrous is not inherited but is due to external influences. Van Scheer studied 348 Mongolian idiots and concluded that heredity played no essential part in the origin of these abnormal babies. He believes that a disturbance in the development of the amnion arises from an improper implantation of the ovum in an abnormal uterine mucosa. Malpas investigated 294 malformed fetuses and found that "in the whole series there was only one instance of a

*Read at the *Fifty-First Annual Meeting of the American Association of* Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

malformation with a known hereditary bias." Hirst says, "To summarize present knowledge of the probable fundamental causation of monsters, it is fair to state that faulty implantation of the ovum probably due to insufficient preparation of the uterine mucosa by follicular and luteal hormones, plus mechanical and chemical environmental influences must be held accountable rather than inherent germ tendencies." Petersen's analysis of his huge statistical data led him to conclude that, "The observations tend to support the suggestion of Mall that these lethal malformations are due to early environmental disturbance." Szendi reported two cases of single ovum twins in which one child was normal but the other was a monster. These monsters were definitely due to intrauterine conditions.

Everyone is familiar with the experimental production of monsters beginning with E. G. St. Hilaire in the early nineteenth century and continuing down to modern times. Particularly noteworthy is the work of Stockard who reduced all abnormal developments to a single factor, namely developmental inhibition or arrest. Stockard said, "All monsters are the result of the same cause and the type of monster depends upon the time at which the cause was in operation."

More evidence in support of the importance of environment in the production of deformed embryos comes from a study of tubal pregnancies. Von Winckel believed that fully one-half of the fetuses in ectopic pregnancy were deformed. Mall found that 96 per cent of ova obtained from tubal pregnancies were abnormal. On the other hand, pathologic embryos were present in not more than 7 per cent of all intrauterine pregnancies early and late. On the basis of this vast difference (96 versus 7 per cent), Mall says, "It seems to me that the argument against the germinal theory of pathologic ova and monsters is overwhelming—pathologic embryos are nothing but young monsters."

Stockard has shown that single ovum twins as well as all nonhereditary malformations are due to properly timed developmental arrests. (It may be emphasized here that the tendency to produce double ovum twins which are in reality not twins at all, is often hereditary. On the other hand, single ovum twinning is not directly inherited but is the result of immediate environmental influence on the course of development.) Stockard's conclusions are based upon animal experimentation but Arey maintains that these concepts, "should apply equally well to human abnormalities and twinning provided the ovum is subject to delay before implantation and to arrest afterward. There is ample evidence for both conditions in the tube." Arey pointed out that the same conditions that induce or accompany tubal implantation also appear to favor twinning, for tubal twins occur about fifteen times more often than twins in uterine pregnancies.

It is generally agreed that in most cases of ectopic pregnancy the decidual reaction is poorly developed. Since the decidua supplies not only a place for the fertilized ovum to implant itself, but also nourishment for the growing ovum, the high incidence of abnormal embryos and twins in ectopic pregnancies may be due to the insufficient decidual reaction which is present in the tube.

PLACENTA PREVIA

By placenta previa we mean a condition in pregnancy in which part or all of the placenta lies in the isthmus of the uterus. The isthmus of the uterus differs markedly from the corpus anatomically, physiologically and biochemically. The musculature of the isthmus is not as well developed as in the corpus, the endometrium contains fewer glands and there is less stroma than in the body of the uterus. The isthmus has a separate blood supply. During labor it forms the zone of dilatation, whereas the function of the corpus is that of contraction. The isthmus does not react to hormones, hence it does not develop a true premenstrual hypertrophy or a predecidual compacta. Furthermore,

Simon has shown that even in cases where the glands of the isthmus show some dilatation in the premenstrual period, there is no glycogen present or only a small amount. Since glycogen is nourishment for the early ovum its absence may account for the infrequency of embedding of an ovum in the isthmus. Likewise, when a fertilized ovum is implanted in the isthmus or when part of the placenta develops in the isthmus thereby producing a placenta previa, an embryo may develop abnormally because of the deficient decidua, just as occurs in tubal pregnancy. If this supposition is correct there should be more fetal monsters and deformities and twins in cases of placenta previa than in cases of implantation of the placenta in the corpus uteri. Strassmann, Essen-Moeller and Irving have each reported that twins occur much more often in cases of placenta previa than otherwise. Furthermore, Strassmann and Roggenkaemper have each shown that babies associated with placenta previa are relatively underweight for their length. Another difference between placenta previa babies and others is the male:female sex ratio. Wesselink reports that in 980 cases of placenta previa in Holland, the male:female sex ratio was 124:100 instead of the normal 105:100. He believes this is due to the deficient decidual reaction in the lower uterine segment with consequent defective nourishment of the embryo.

CLINICAL DATA

To determine statistically whether or not monsters occur more often in cases of placenta previa, I wrote to many clinics chiefly in the United States but also a few in Canada and Great Britain. I received information from 26 clinics concerning 369,597 labor cases and from 14 additional clinics concerning their placenta previa cases. Among the 369,597 labor cases there were 3,474 fetal deformities, an incidence of 0.94 per cent (Table I).

Mall claimed the incidence of all deformed embryos and fetuses for intrauterine gestations was 7 per cent. However, most of these deformed embryos were expelled spontaneously as miscarriages early in pregnancy. The incidence of fetal monsters at term was only 0.6 per cent. Mall found that "three well-formed monsters are aborted in the early months of pregnancy for every one which goes to the end of pergnancy."

Guttmacher has shown that twins occur more than twice as frequently in abortions as in pregnancies which go to viability. Most likely a frequent cause of spontaneous miscarriage in the early months of gestation is placenta previa. Were these interrupted pregnancies to continue to term the incidence of fetal deformities in all pregnancies but especially in cases of placenta previa would be far greater than it is.

In the 40 clinics from which I obtained data, there were 3,423 cases of placenta previa and among these cases there were 94 fetal monsters, an incidence of 2.75 per cent (Table II). Thus the incidence of abnormal babies was almost three times as high in the placenta previa cases as in the entire 369,597 cases (2.75 versus 0.94 per cent).

I found in the literature seven articles in which the number of deformed babies in large series of placenta previa cases was quoted (Table III). The total number of placenta previa cases in these reports was 1,023 and the number of fetal monsters among these cases was

17. If we add these 1,023 placenta previa cases to the 3,423 cases I collected, the total number of cases of placenta previa analyzed by me amounts to 4,446. The entire number of deformed babies in the combined series amounts to 111. Hence, among the 4,446 cases of placenta previa the incidence of deformed children was 2.5 per cent (Table IV). This figure is between 2½ and 3 times as high as the incidence of fetal deformities in the 369,597 cases.

TABLE I

INSTITUTION	NO. OF LABOR CASES	NO. OF FETAL DEFORMITIES
Philadelphia Midwives (Nicholson)	96,500	192
Chicago Lying-in Hospital	35,179	611
Johns Hopkins Hospital (Manahan)	32,000	224
Elizabeth Steel Magee Hospital (Ziegler)	23,958	305
Edinburgh Royal Maternity (Sturratt)	22,740	198
Margaret Hague Hospital (Cosgrove)	21,433	393
Cook County Hospital	16,242	48
Chicago Maternity Center (Tucker)	14,315	48
Lewis Memorial Hospital—Chicago (Fortin)	13,261	129
Woman's Hospital—Detroit (Daniels)	11,122	176
Lying-in Hospital—New York (Stander)	10,099	287
Woman's Hospital—New York (Barrett)	9,623	161
Royal Victoria Hospital—Montreal (Fraser)	9,194	66
Methodist Episcopal Hospital—Brooklyn (Matthews)	8,617	226
Cedars of Lebanon Hospital (Lazard)	6,514	62
Carney Hospital (Phaneuf)	6,428	10
Stanford Univ. School of Med. (Fluhmann)	6,279	8
Multnomah Hospital (Holman)	5,693	38
Bellevue Hospital (Freed)	4,030	26
University of Southern California (McNeile)	3,779	80
University of Michigan (Miller)	3,447	119
Indianapolis City Hospital (Beckman)	2,500	9
Wesley Hospital—Chicago (Serbin)	2,040	4
M. P. Rucker (Richmond)	1,579	12
University of Wisconsin (Harris)	1,612	22
St. Margarets Hospital—Pittsburgh (Titus)	1,313	20
	369,597	3,474, 0.94 per cent

The incidence of fetal deformities in cases of placenta previa most likely would be much higher than it is were it not for the fact that there are two types of placenta previa. In the first type, the ovum is implanted in the lower part of the body of the uterus and a portion of the placenta grows down into the lower uterine segment. In the second type, the ovum is primarily implanted in the isthmus. In the first group of cases, there is ample nourishment for the growing ovum, hence little chance for the development of a monster. In the second group, however, the decidual reaction is incomplete and hence there is a much greater likelihood for the development of an abnormal fetus. Fortunately the second group is much less common than the first, else there might be a greater incidence of fetal deformities.

In emphasizing the relationship of the lower uterine segment to fetal deformities, I am not unmindful of the fact that the actual total number of monsters in pregnancies situated in the body of the uterus is far

TABLE II

INSTITUTION	NO. OF PLACENTA PREVIA CASES	NO. OF FETAL DEFORMITIES
Edinburgh Royal Maternity (Sturratt)	531	5
London Hospital for Women (Davies)	481	8
Elizabeth Steel Magee Hospital (Ziegler)	247	3
Johns Hopkins Hospital (Manahan)	222	10
Chicago Lying-in Hospital	194	12
Margaret Hague Hospital (Cosgrove)	149	4
Cook County Hospital	140	10
Toronto General Hospital (Scott)	132	7
University of Minnesota (Litzenberg)	100	0
Woman's Hospital—New York (Barrett)	89	2
University of Southern California (McNeile)	80	1
Hospitals of Memphis (Reinberger)	75	2
Woman's Hospital—Detroit (Daniels)	66	1
Cleveland Maternity (Bill)	65	4
Cedar Rapids—Iowa (Brown)	62	2
Evanston Hospital (Smith)	60	1
Lying-in Hospital—New York (Stander)	58	4
University of Michigan (Miller)	56	6
University of Rochester (Wilson)	56	0
Royal Victoria Hospital—Montreal (Fraser)	48	0
Lewis Memorial Hospital—Chicago (Fortin)	47	4
University of Kansas (Calkins)	47	0
Methodist Episcopal Hospital—Brooklyn (Matthews)	45	1
Multnomah Hospital (Holman)	44	0
Cedars of Lebanon Hospital (Lazard)	38	0
Stanford U. Med. School (Fluhmann)	35	0
Louisville City Hospital (McConnell)	34	3
University of Iowa (Plass)	30	0
Richmond, Va. (Rucker)	29	0
Indianapolis City Hospital (Beckman)	27	0
Bellevue Hospital (Freed)	25	1
Sibley Memorial Hospital—Washington (Kotz)	24	0
Chicago Maternity Center (Tucker)	21	2
British Post Graduate School (Moir)	21	1
Wesley Hospital—Chicago (Serbin)	12	0
George Washington University (Kotz)	12	0
University of Wisconsin (Harris)	11	0
St. Margarets Hospital—Pittsburgh (Titus)	10	0
	3,423	94, 2.75 per cent

TABLE III

AUTHOR	CASES OF PLACENTA PREVIA	NO. OF DEFORMITIES
Irving	308	2
Genova	285	5
Arnold	173	3
Siegel	101	3
Lieberman	79	1
Edinburgh Maternity	41	2
Ekas	36	1
	1,023	17

greater than the number of defective babies in the lower uterine segment. This, of course, is due to the fact that corpus pregnancies occur about 1,000 times more frequently than cases of placenta previa (DeLee, Williams). However, whereas abundant and healthy decidua is found in the vast majority of pregnant uteri, there are instances where for one reason or another the decidua is defective. When ova are implanted in such uteri with defective decidua, deformed babies may result. The occurrence of abnormal decidual reaction may explain why women who give birth to monsters frequently have miscarriages, premature labors,

TABLE IV. SUMMARY

Total number of labor cases	369,597	
Number of deformed babies	3,474	
Incidence of deformed babies		0.94 per cent
Total number of placenta previa cases in forty clinics	3,423	
Number of deformed babies	94	
Incidence of deformed babies		2.75 per cent
Total number of placenta previa cases in forty clinics and literature	4,446	
Number of deformed babies	111	
Incidence of deformed babies		2.5 per cent

and stillbirths shortly before and after the birth of abnormal babies. It may also account for the relative sterility which often occurs just before a malformed baby is born because the decidual reaction may have been insufficient to permit implantation or development of a fertilized ovum. Furthermore, defective decidua may be responsible for the repetition of the same or different types of malformed babies in the same woman, because the abnormal decidua may be present in repeated gestations. Defective children occur much more often in women past forty years of age than in young women. This may be due to the fact that many women who reach forty years of age have gone through a number of full-term pregnancies, miscarriages, and perhaps intrauterine manipulations, such as curettements, manual removal of the placenta, and so on, any or all of which may have resulted in a localized or generalized disturbance in the endometrium.

These ideas are contrary to the belief of Murphy who said, "Reproductive inefficiency was indicated by (a) the long period of relative sterility frequently observed immediately preceding the birth of the malformed child, (b) the nearness of miscarriages, premature births and stillbirths to the malformation pregnancy, (c) the high incidence of malformed offspring born to older mothers, and (d) the increased frequency of congenital defects among brothers and sisters. Since these evidences of reproductive weakness, in very many cases, operated over a period of years, it seems likely that their origins rested upon defects within the germ cells, rather than upon abnormality in the environment."

In support of my contentions and opposed to Murphy are the statements of the embryologists and others quoted in the first part of this present paper and also the following quotations.

Malpas says, "The frequency with which a given malformation was followed later by another type of malformation appeared to show from another standpoint that most of the malformations dealt with could not be due to the action of specific

groups of genetic factors and reinforced the view that they are mostly attributable to the interplay of environmental factors.'' Van der Scheer says, ''In mothers of Mongolian idiots there must be an inhibiting factor of progenitor, the origin of which supposedly must be ascribed to an affliction of the uterus or the uterine mucosa. . . . The cause must be found in the mother because in families with Mongolian idiots there are many miscarriages, fetal deaths, and monsters and there is a long interval between the Mongolian idiot and the previous birth of a live child. The Mongolian idiot is not only often the last born but also a late comer.'' Greig in discussing localized congenital defects of the scalp says, ''Moreover heredity is not a factor, though more than one child in the same family may be affected.''

The 4,446 cases of placenta previa may seem to be a small number of cases on which to base conclusions but when we realize that placenta previa occurs approximately once in a thousand labor cases in general practice, the 4,446 cases represent about 4,000,000 cases.

In some clinics the difference between the incidence of monsters in the cases of placenta previa and all the obstetric cases is striking. For example in the old Chicago Lying-in Hospital with which I was associated, there were 35,179 babies born from July 1, 1918 to June 1, 1931, when the hospital was closed. There were 611 fetal monsters in this series, an incidence of 1.7 per cent. On the other hand, among the 194 cases of placenta previa observed in this institution during the same time there were 12 monsters, an incidence of 6.2 per cent. All of the monsters were dead on delivery or died shortly afterward. There were six babies with anencephalus, two with spina bifida, two with eventration of the viscera, one with hydrocephalus, and one with scleroderma neonatorum (Hospital Nos. 11421, 17158, 20409, 24377, 24997, 26695, 58706, 58771, 63991, 66662, 70710, 79799).

The increased frequency of fetal monsters in cases of placenta previa has more than academic interest. First, dangerous and even fatal bleeding may result from placenta previa associated with a hydrocephalus if the latter is not recognized and delivery is forced through the vagina. Second, more and more cesarean sections are being performed throughout the world for placenta previa. It is most uncomfortable to deliver an unrecognized fetal monster by cesarean section, especially if the abdominal route was urged by the physician in order to secure a live baby. Fortunately, in a large proportion of cases of placenta previa, it is possible to detect fetal monsters in utero, if not by physical then by x-ray examination.

In the paper which I wrote on this subject in 1923, I found that 12 of the 21 monsters mentioned in that paper had cranial defects. In my present data I have knowledge of the type of deformity in 67 cases. There were 19 babies with anencephalus, 7 with hydrocephalus and 10 with spina bifida. The anencephalic and hydrocephalic babies can often be detected by physical examination but certainly by means of roentgen ray pictures. Furthermore, as I suggested in 1923, spina bifida may also be detected on x-ray plates if this anomaly is specifically looked for. Hence, approximately half of the monsters associated with placenta previa can be determined before delivery.

The practical lesson, therefore, is that we should bear in mind the increased frequency of fetal deformities in cases of placenta previa and

take an x-ray picture of such a patient. By this means many fetal monsters will be found which otherwise would have been overlooked. In most of these cases conservative means of delivery will be employed. In some cases, however, cesarean section will be the safest treatment for the mother notwithstanding the presence of a monstrosity.

SUMMARY

In this paper I have attempted to show that fetal monsters and deformities occur more frequently in cases of placenta previa than otherwise. Evidence has been presented from embryologists and others to show the great role played by environment in the etiology of monsters. Clinical data to support this are obtained from the very high incidence of malformed embryos and twins in cases of tubal pregnancy where the decidual reaction is only slightly developed. Likewise, it is pointed out that the decidual reaction in the isthmus of the uterus is poorly developed and that this plays a role in the causation of abnormal fetuses in cases of placenta previa. I collected data covering 369,597 labor cases and found that whereas the incidence of fetal monsters was 0.94 per cent for the entire group, the frequency of fetal deformities in the 3,423 cases of placenta previa in essentially the same group was 2.75 per cent. If to these 3,423 cases are added 1,023 cases of placenta previa which I collected from the literature, the incidence of fetal monsters and deformities for the entire group of 4,446 cases of placenta previa (representing approximately 4 million obstetric cases) was 2.5 per cent as contrasted with 0.94 per cent for all obstetric cases.

In approximately half of all the abnormal fetuses associated with placenta previa, the deformity consisted of defects which can easily be recognized by means of x-ray pictures. Hence, in every case of placenta previa an x-ray picture should be taken. The detection of fetal monsters will usually lead to conservative treatment although cesarean section will have to be employed in some cases in spite of the fetal abnormality.

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55 EAST WASHINGTON STREET

DISCUSSION

DR. R. M. H. POWER, MONTREAL, QUE.—Environment in relation to the production of monsters must be regarded from the angle of "soil and nutrition"; these are really synonymous terms and are under endocrine control. The endometrium in its secretory phase is the result of endocrine stimuli, and represents the total of endocrine synchronization for that particular month, i.e., the united efforts of the pituitary, thyroid, and the ovary. The influence of imperfect nidation may affect the whole after life of the fetus, and nidation depends upon two factors. First, the ability of the trophoblast to open up maternal sinuses. Second, the susceptibility of the maternal tissues to be opened up. This susceptibility depends upon estrogenic and luteal factors. Therefore, all environmental fetal deformities must trace their origin to one or both of these factors.

Not all portions of the endometrium are affected to the same degree at the same time; thus we may find side by side in the same endometrium, as shown by my slide, advanced stages of preparation, with other areas of decided lack of preparation.

The results of animal experimentation should apply to human abnormalities. A student of animal husbandry recently stated, "Over 98 per cent of hens' eggs are normal, and if properly fertilized will generate a normal chick if circumstances of environment are normal." We must realize from the above statement, that the great majority of teratomatous growths are due to faulty preparation of the soil.

Stockard and others have shown that a reduplication of embryonic parts, may be brought about experimentally by a temporary arrest of embryonic development at a critical growth period. When a growing apical bud of a twig is arrested in development by pinching off or other methods, dichotomous growth occurs and as a result the two adjacent axillary buds, quiescent during the supremacy of the apical bud, begin to develop twin branches. Similarly the same author has produced a reduplication of parts and marked degrees of twinning in trout embryos, by arresting the development at a critical growth period.

DR. J. K. QUIGLEY, ROCHESTER, N. Y.—Dr. Greenhill has made out a strong case for a greater frequency of fetal deformities in the cases of placenta previa. The reason he advances is very plausible, namely faulty implantation due to imperfect decidual reaction which is more common in case of placentation in the lower uterine segment.

Dr. Greenhill's estimate of 2.5 per cent frequency in placenta previa as against 1 per cent in all pregnancies, while it means that this frequency is two and one-half times, nevertheless means that 97½ per cent of babies born to mothers with placenta previa do not have congenital deformities and abnormalities, so that from a practical standpoint it is not of great importance and I do not believe it sufficient to demand x-ray examination of all cases of placenta previa subjected to cesarean section.

If this form of delivery offers the better prognosis for the mother in some cases, particularly in placenta previa in the primipara and in cases of the central or complete variety, I would not be deterred from this course in the interest of the mother even with a 2.5 per cent chance of obtaining an anencephalic monster any more than I would hesitate to deliver by the abdominal route the occasional case of ablatio with the knowledge that the child had perished, if I thought the chances for the mother were better than by delivery through the pelvis.

A review of the records of the Rochester General Hospital since 1926 revealed 71 cases of placenta previa and in none of these were any congenital deformities found.

There is an interesting parallel in the correlation between anencephalic monsters and hydramnios, acute and chronic. Inasmuch as the cause of hydramnios has never been satisfactorily established, the association of these two conditions is not as easily explained as is the coexistence of placenta previa and fetal deformities. This association of hydramnios and deformities I believe to be much higher than 2.5 per cent.

DR. EVAN SHUTE, LONDON, CANADA.—A good placental foundation ordinarily appears to depend upon the balance in the maternal organism between the invasive qualities of the chorion and the powers resisting chorionic aggression (to borrow Dr. Montgomery's picturesque term). Vitamin E appears to favor villous penetration of the uterine wall and estrogens to resist it. Therefore it is interesting to speculate upon just what is the effect of vitamin E on the origin of monsters.

Recently I had occasion to collect the data in the literature on the fetuses delivered after threatened abortion had been successfully controlled until at least the fifth month by means of vitamin E or its cousinly hormone, progesterone. Of 443 patients so treated only 2 per cent expelled deformed fetuses. If the idea so generally held—viz., that most aborting fetuses are defectives—be true, one can scarcely escape the conclusion that vitamin E and progesterone may actually facilitate a completion of the inadequate development of certain types of defectives if given in time.

In this connection it is interesting to recall Peterson's observation that very few abnormal fetuses are conceived in Chicago in the months of July, August, and September each year. Although this does not appear to be borne out in Philadelphia, according to Murphy's intensive survey, it is true for our part of Western Ontario. As it is in these months that most vitamin E is available in green diets, there may be a correlation between E deficiency and the conception of anomalous fetuses. Hence the biologic significance of such established folk customs as June weddings.

Moreover Peterson's map of the United States showed that the incidence of abnormalities decreased as one went toward the south. Peterson held that barometric pressure was the significant factor in this phenomenon, but I would suggest that dietary variation was the more probable cause.

The problem is not easy to settle experimentally, since such experimental animals as rats, at least, appear to be too well integrated somatically for any disruptive influence of an E-deficient diet to be revealed. However, I have found two hydrocephalic young in the litters of rats on E-low diets and the occurrence of hydrocephalics and cretins in such litters has also been reported by Barrie in England. Possibly more highly organized forms such as man may more easily display a greater variety of response to such vitamin deficiency.

At present we are trying to collect data on women whose only previous conceptions have all ended in the birth of defectives, and whom we can treat with vitamin E from the beginning of later pregnancies. We have only 4 such cases to date, of whom 3 have completed their pregnancies and had normal children. Such a series when much larger may prove significant.

DR. GREENHILL (closing).—Cesarean section will often have to be done notwithstanding a monstrosity because this operation is usually performed for the sake of the mother and not for the child. In cases of partial placenta previa, delivery through the vagina should be carried out when there is knowledge of a deformed baby.

About eighteen years ago while doing some work at the Carnegie Institute in Baltimore with Dr. Streeter, I had an opportunity to learn a good deal about embryos and young fetuses. A relatively large proportion of fetuses expelled spontaneously were found to be abnormal. Because of this knowledge I have always been hesitant about using progesterone in cases of threatened abortion for fear that full-term monstrosities might result. However Shute's information about the 344 cases of threatened abortion with only a 2 per cent incidence of fetal monsters is remarkable. Undoubtedly vitamin E must have played some part.

MATERNAL AND FETAL EXPECTATIONS WITH MULTIPLE PREGNANCY*

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THIS study is offered for three reasons: first, as response to aroused public interest in plural births due to survival of several recent American† and two British‡ quadruplets, and of course the Canadian Dionne quintuplets, to indicate what may reasonably be expected from the occurrence of multiple pregnancy; second, to show that the accident of more than one birth at a single confinement should be anything but a matter of the usual amazement and chagrin to the physician, astonishment and dismay to the parents and amusement to everybody else; and third, to offer personal comments on toxemia of pregnancy as seen in twins and triplets.

The material presented is a brief summary of the literature concerned with unusual complications seen in plural births, as well as leading articles bearing upon our statistics, which are derived from 223,394 total births beyond sixteen weeks' gestation in the City of Philadelphia in the seven years from 1931 to 1937 inclusive, as obtained from the Municipal Bureau of Vital Statistics. From these are obtained through the Philadelphia Maternal Mortality Committee (Philip F. Williams, M.D., Chairman) the plural births among 1,469 puerperal deaths from all causes as well as 835 deaths excluding those associated with abortion, miscarriage and ectopic gestation. To these groups are added detailed progress of 3 sets of triplets and 219 pairs of twins out of 19,463 total births beyond twenty weeks' gestation in the Philadelphia Lying-in Hospital from July 1, 1929, to June 30, 1938; 1 set of triplets and 60 pairs of twins out of 5,483 births in the Maternity Department of the Hospital of the University of Pennsylvania from 1931 to 1937 inclusive, and a recent "experimental" group comprising one set of triplets and 26 pairs of twins from the last 2,000 births in the Preston Retreat, Philadelphia.

The scope of the study does not include speculation on the cause or mechanism of twinning or on the accuracy of reported habitual litters as evaluated by Greulich;[1] or on differentiation and biologic differences and relative frequency of single and double ovum twins, race, recurrence and age, so well described by Guttmacher,[2] but is concerned chiefly with results seen in plural births.

*Read, by invitation, at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

†Mullins, mixed, aged 1 year, Porter, Okla.; Kasper, mixed, aged 2½ yrs., Passaic, New Jersey; Schense, mixed, aged 7 yr., Aberdeen, S. D.; Morlok, females, aged 8 yr., Lansing, Mich.; Perricone, males, aged 9 yr., Beaumont, Texas; Keyes, females, aged 23 yr., Hollis, Okla.

‡Taylor, mixed, aged 3 months; Mites, aged 3 years.

CITY OF PHILADELPHIA STATISTICS

Maternal Results.—In this large series, in addition to giving the maternal death rate from all puerperal causes, we added an additional rate obtained by deducting deaths associated with abortion, miscarriage, and ectopic gestation for comparison with the twin birth death rate over 16 to 20 weeks' gestation. This was done because many multiple pregnancy miscarriages are overlooked, and because the literature shows only 65 unilateral and 43 simultaneous bilateral ectopic twin pregnancies (Falk and Blinick,[3] Levine,[4] Pudney,[5] Ferguson,[6] Siegler,[7] Lull[8]). It is apparent from

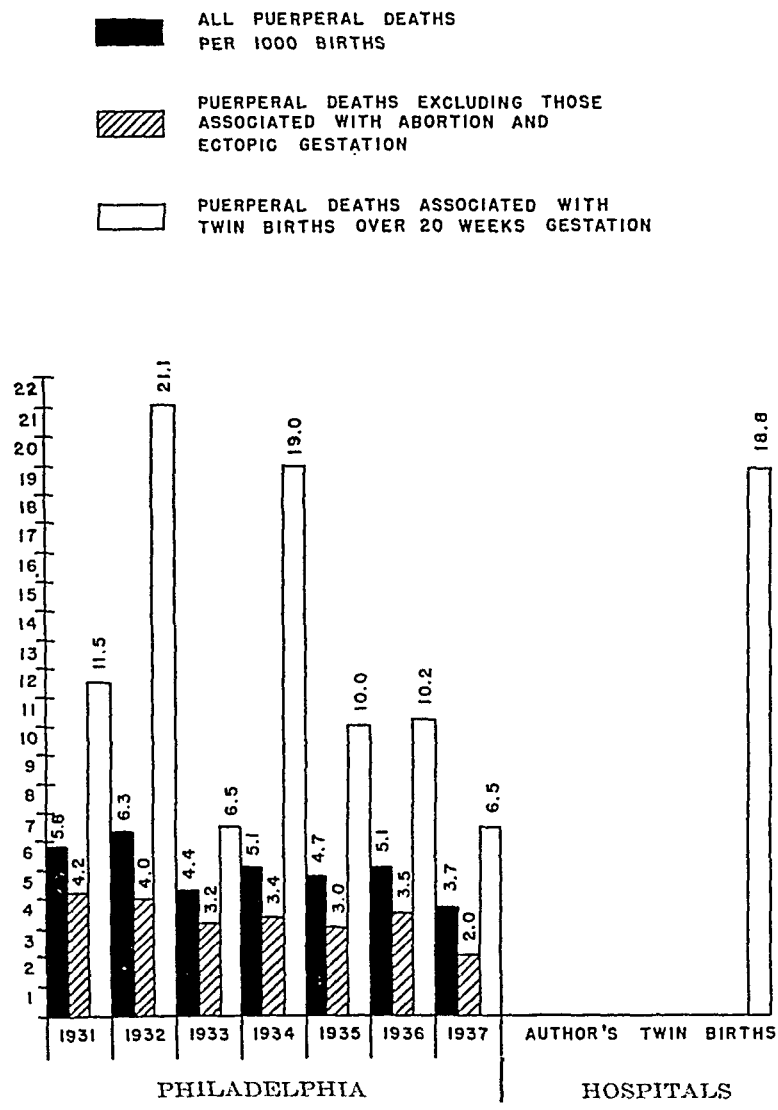


Fig. 1.—Maternal mortality rates in Philadelphia during the last seven years, showing an average of 1.21 per cent for twin births, 0.50 per cent for all puerperal deaths, and 0.33 per cent excluding abortions and ectopic gestations, compared to 1.88 per cent for 279 twin births in the Lying-in and University of Pennsylvania Hospitals.

Fig. 1 that the average maternal death rate (1.21 per cent) associated with plural births over sixteen weeks' gestation, during the last seven years, was three times the average rate (0.50 per cent) for the total puerperal deaths and over four times as great as the average rate (0.33 per cent) for maternal deaths excluding abortion, miscarriage, and ectopic gestation. At this point, it may be stated that Philadelphia experienced no quadruplets over 16 weeks' development, but from the three years 1934 to 1936, inclusive, there were seven known triplet births[9] (1:13,253) and in the remaining four years, 16 calculated (1:8,000) additional, but there were no *maternal deaths associated with these 23 triplet births.*

Splitting up the twin deaths according to Fig. 2 shows that, whereas the normal incidence of viable twin births averages under 1:90 (1:100+ in our Philadelphia series), the frequency was doubled in the septic and cardiac deaths, quadrupled in the late gestational toxemic, and increased to the amazing frequency of 1:18 in the postpartum hemorrhage fatalities. It is obvious therefore that in spite of the fact that in Philadelphia 80 per cent of all patients to be confined are hospitalized, each woman with multiple pregnancy assumes risk sufficiently great as to require extraordinary precautions suggested later.

Infant Results.—Only the general stillbirth (over 16 to 20 weeks) rates and the neonatal death (over 28 weeks or 1,500 gm.) rates for the years 1931 to 1937 inclusive (Fig. 2) can be presented for the entire city of Philadelphia, since the Still-

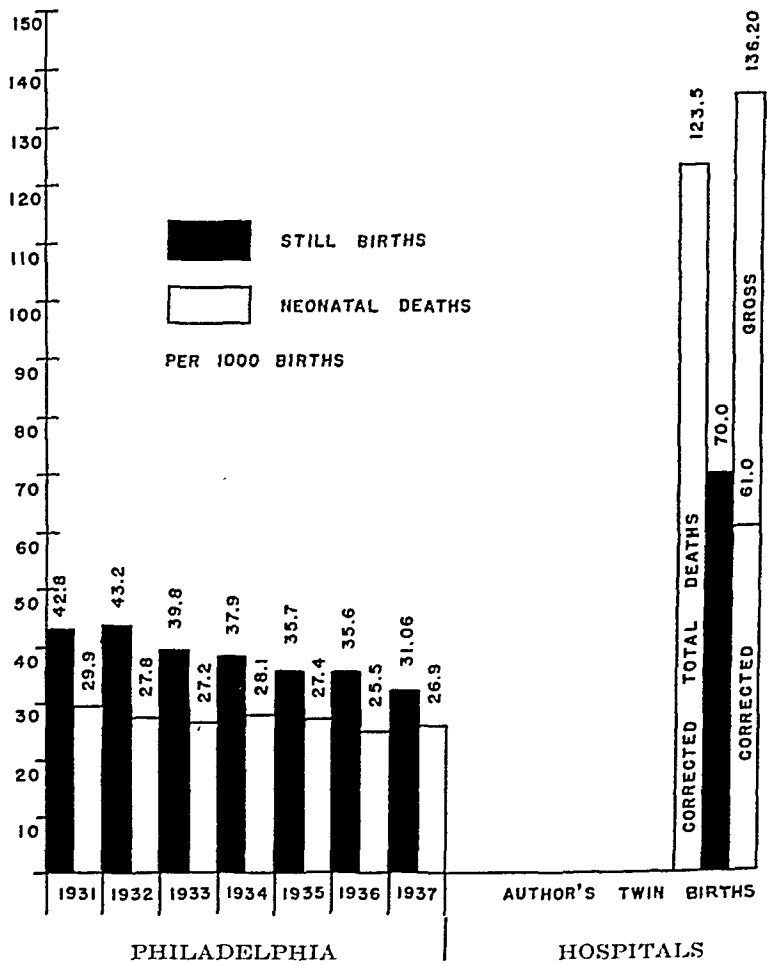


Fig. 2.—Comparison of gross stillbirths and neonatal deaths over sixteen weeks in Philadelphia with rates among 558 twins in the Lying-in and University of Pennsylvania Hospitals.

birth Committee of the Philadelphia Obstetrical Society (chairman, Thaddeus Montgomery, M.D.) and the Neonatal Death Committee of the Department of Health (chairman, Ralph Tyson, M.D.) are of recent origin and have not yet reported causes of their respective deaths. The above rates, like the general maternal rates, show a gradual decline with a seven-year average of 3.8 per cent for stillbirths, and 2.75 per cent for neonatal deaths (total 6.55 per cent), which is roughly one-half the respective rates (gross 7.0 per cent and 13.62 per cent; corrected 6.27 per cent and 6.1 per cent) among 558 twins in the author's hospital series. The latter, totaling 12.37 per cent (corrected), show a reversal of the two types, indicating that prematurity is of greater importance in the postnatal than in the natal period of the infant's existence.

THE LYING-IN, UNIVERSITY OF PENNSYLVANIA AND PRESTON RETREAT HOSPITAL SERIES

Since there were but five instances of triplets, these may be disposed of briefly at this point according to a recent report:[10] toxemia in one mother, post-partum hemorrhage in another, and severe endometritis in a third, but all labors and deliveries easy, due to marked prematurity in each case. One infant was stillborn, four died within a short time and probably the sixth. Since that report, one additional set of syphilitic triplets in the twenty-sixth week of gestation has been confined as an emergency undiagnosed case in the Lying-in Hospital without dystocia or other complications, delivering spontaneously with only twenty-five minutes between infants which were all females and weighed 1 pound 4¾ ounces; 1 pound 4¾ ounces, and 1 pound 4 ounces, all of whom died in a few hours, and combined with the above triplets yield an infant mortality of over 50 per cent.

Progress of twin pregnancy and infants from the first two hospital services, representing 95 per cent registered confinements, are combined and will be described under five headings, namely: pregnancy, labor, delivery, puerperium, and infant.

1. *Pregnancy.*—Among 279 double pregnancies of twenty weeks' gestation or over, there were but 40 primigravidas, the average being gravida 3.8. The duration of pregnancy averaged 35.4 weeks from the first day of the last period, which partly accounts for the fact that only 99 duplications were diagnosed before labor, 20 in labor and 160 or the majority as late as birth. The earliest diagnosed case was that of twins in one horn of a double uterus at thirteen weeks by the author by means of double ballottement and relatively increased urinary anterior pituitary-like excretion. Roentgenography confirmed the diagnosis in 58 cases, proved the only means of diagnosis in 24, was not utilized at all in the great majority or 195, and was erroneous in 2 of the pregnancies, which were classified as: private 34; registered ward 219; registered student out-service 10; and emergency or unregistered 15 (5.4 per cent).

Complications.—Excess weight was frequent, the greatest amounting to 70 pounds (200 to 270 pounds), which according to Matthews[11] when over 200 pounds predisposes to excess kidney, liver, and heart stress, prolonged labor in the majority, some type of complication in 75 per cent, and malposition in 26 per cent of all such cases. Toxemia appeared 37 times as pre-eclampsia (14 quite "mild," and 2 superimposed on nephritis), 3 times as eclampsia, and only 7 times as hyperemesis. If to the mild pre-eclamptics may be added 12 instances of considerable edema only, we obtain a picture simulating low reserve kidney (Stander's[12] temporary disorder distinct from all nephritides, not distinguishable from "mild pre-eclampsia," featured by slight hypertension and albuminuria and occasional slight edema in young nulliparas, and recurring in only one-half of subsequent pregnancies), which this author attributes to the usual decided abdominal tension common to both first and multiple pregnancies, and resulting probably in either renal ischemia or ureteral distortion. This theory is further suggested by the fact that from 40 single viable pregnancies subsequent to twin births reported in our series of whom 8 had experienced toxemia, only 3 showed recurrent toxemia.

On the other hand, if lateral ureteral pressure, deviation or other obstruction be related to late gestational toxemia, it should be especially apparent in multiple pregnancies, yet only 4 of our 279 twins showed obvious ureteral pain and/or infection. This is neither in agreement with original data obtained by the author in 1929,[13] when from many cystoscopic investigations in 2,101 pregnancies appeared 140 (6.6 per cent) cases of proved pyelitis, mostly of the infected hydronephrotic group, and 23 cases of extreme simple hydronephrosis both in much greater proportion among 44 cases of hyperemesis and 232 cases of late gestational toxemia than among the normal pregnancies; nor in agreement with Peter's and Zimmerman's[25] later data on the relation of pyelitis to toxemia of pregnancy. From this we concluded that ureteral-renal embarrassment of some sort including distal ureteral congestion and/or edema was related to gestational toxemia, and having found extreme tempo-

rary bilateral hydronephrosis and *relatively* normal estrogen and anterior pituitary-like excretion[26] in a triple pregnancy complicated by very mild late gestational toxemia at thirty-eight weeks,[9] we continue in this belief, discounting the infrequency of ureteral symptoms in the present twin series on the basis of lack of present cystoscopic facilities maintained in and by the two maternity departments concerned. A final comment on the common edema of late twin pregnancy is the significance of change of blood volume which is increased 26 per cent in normal single late pregnancy[14] and greatest of all in twin pregnancy,[15] all of the aforementioned ideas being apparently opposed to but not incompatible with the generally accepted general-arteriolar-spasm mechanism in late gestational toxemia.[16]

Syphilis played its usual part, affecting 17 or 6.1 per cent of the mothers; severe cardiac deficiency affected 14, while placenta previa and partial abruptio placentae endangered, respectively, 5 and 3 pregnancies, yet there were no prenatal deaths.

2. *Labor.*—Labor began and continued spontaneously towards the second births in 193 of the cases; medical induction was utilized 24 times, and failed only 9 times. Excluding podalic version, the membranes of the first sac were artificially ruptured 14 times, of the second 45 times; and surgical induction was required only 4 times. Only 27 instances of dystocia were noted, with an average duration of 23.4 hours in such cases. In spite of frequent polyhydramnios and malposition, prolapsed umbilical cord was noted only once before birth of the first twin.

Analgesia in the form of morphine sulphate was given 46 times, the maximum dose was ¼ gr., twice; as pentobarbitol sodium 48 times, maximum dose 9 gr., average 6 gr.; and as miscellaneous sedatives 4 times, the heaviest being alurate 10 gr., so that narcosis cannot be responsible for the high fetal death rates.

3. *Delivery.*—Both infants were delivered spontaneously 51 times, the first 67 times and the second only 13 times, making 182 spontaneous births out of 558 deliveries (31.1 per cent), and by contrast cesarean section was performed 12 times (4.3 per cent). Forceps assistance was utilized 85 times for the first child and 12 times for the second; version, 6 times for the first and 125 times for the second; and breech extraction 54 times for the first and 70 times for the second, this high frequency (68.9 per cent) of interference accounting for a low average time-interval between births of 13.1 minutes, including a maximum wait in one case of eight and one-half hours.

Hemorrhage during birth was not fatal but severe in 12 (4.3 per cent) women, once due to placenta previa, 3 times due to abruptio placentae between infants, and 8 times before delivery of the placenta. The very nature of twin births and both of our groups of statistics indicate frequent hemorrhage from low placental implantation or premature separation, yet several recent case reports in the literature[17-19] would suggest rarity of such bleeding. Prolapse of the umbilical cord between births occurred 4 times, whereas one cord was so short as to require high forceps for delivery.

4. *Puerperium.*—Post-partum hemorrhage was serious in 15 cases (5 per cent), for whom 21 transfusions were essential and for as many more might well have been

TABLE I. INCIDENCE OF TWIN BIRTHS IN THE FOUR MOST COMMON CAUSES OF MATERNAL DEATH IN THE CITY OF PHILADELPHIA

CAUSE OF DEATH		NUMBER AND RATIO OF TWIN BIRTHS
Sepsis	255	5 (1:51)
Toxemia and eclampsia	156	6 (1:26)
Hemorrhage:		
A. All types	129	6 (1:21.5)
B. Post-partum	(74)	(4) (1:18)
Heart disease	49	1 (1:49)
Other causes	246	9 (1:27.3)
(Excluding abortions and ectopic gestations)		
Totals	835	27 (1:31)

used, making a total incidence of hemorrhage in pregnancy, labor, delivery, and puerperium of 36 or 13 per cent. The nonfatal and fatal morbidities are listed in Tables II and III and are much higher than for single pregnancy.

5. *Infants.*—The average weights of each pair of babies were 5 pounds 6 ounces for the larger and 4 pounds 9¾ ounces for the smaller, the largest pair weighing 8 pounds 11½ ounces and 8 pounds 1¾ ounces. One hundred eleven were breast fed, 156 weaned completely, and 176 had both breast and bottle, which had no relation to the 39 stillbirths, little relation to the 22 neonatal complications (Table IV) but may or may not have had relation to the 76 total neonatal deaths involving 40 pairs, plus 14 of the larger and 21 of the smaller of pairs according to Table V.

TABLE II. CAUSES OF NONFATAL PUERPERAL COMPLICATIONS IN 279 TWIN BIRTHS OVER TWENTY WEEKS' GESTATION. HIGH INCIDENCE OF ENDOMETRITIS ATTRIBUTABLE TO FREQUENT INTERFERENCE (68.9 PER CENT)

Sapremia	19
Deciduitis	2
Endometritis	22
Parametritis	2
Pyelocystitis	5
Pneumonia	3
Breast engorgement	2
Postoperative	3
Perineal	2
Upper respiratory infection	1
Septic splenitis	1
Total	62 (22.3%)

TABLE III. CAUSES OF DEATH FROM 279 TWIN BIRTHS OVER TWENTY WEEKS' GESTATION

1. Septicemia, peritonitis	
2. Post-partum hemorrhage. (Bilateral hydronephrosis, ascites, pleural effusion)	
3. Hemolytic streptococcic septicemia	
4. Acute dilatation of heart	
5. Abscess of broad ligament, bilateral cellulitis, acute splenic tumor, bilateral pleurisy	
Total	5 (1.88 per cent)

TABLE IV. NONFATAL COMPLICATIONS AMONG 443 SURVIVAL TWINS LISTED BY THE PEDIATRIC SERVICE

Syphilis	3
Club foot	1
Fractured humerus	1
Rickets	2
Convulsions	1
Anemia	3
Pneumonia	1
Pulmonary atelectasis	3
Facial growth	1
Pylorospasm	1
Abscess of anus	1
Congenital heart disease and undescended testicle	1
Hypospadias	1
Microcephaly	1
Hemorrhagic disease	1
Total	22 (5%)

From 165 sets of twins in the Philadelphia Lying-in Hospital, Tyson[20] found nearly 3 times as many twins born in August as in other months of the year, therefore since bi-ovular twins are three times as frequent as uniovular, and since most December twin conceptions would deliver in August rather than September, the question of possible seasonal double ovulation should be considered. From the same source, Tyson[2] also found that multiple pregnancy was the third commonest cause of 469 premature infants (Table VI).

It is noteworthy that among all of the infants, there was but one autositic monstrosity (alimentary atresia) and no instance of omphalositic, parasitic or symmetrical joined twin, and none of combined healthy, macerated and/or papyraceous twins or triplets as reported by Edmunds,[21] Collins.[23] This is of interest inasmuch as in the event of intrauterine death of one uniovular fetus as by hemiplacental necrosis or any other cause, the second should also succumb. With respect to placental anomalies, variable and frequently inadequate descriptions made it impossible to list accurately such rare possibilities as monoamnion,[24] etc.

TABLE V. CAUSES OF 76 NEONATAL DEATHS FROM 558 TWINS OVER TWENTY WEEKS' GESTATION, SHOWING THAT PREMATURITY ACCOUNTS FOR 50 PER CENT

Prematurity		44
Trauma		2
Hemorrhagic disease		2
Erythroblastosis		2
Syphilis		2
Asphyxia		1
Prolapsed cord		1
Cardiac deficiency		2
Atresia of esophagus and anus		1
Pneumonia		1
Doubtful		18
Total		76 (13.62%)
Deductible		
Prematurity	39	
Under 28 weeks		
Under 1500 gm.		
Defects	3	
Corrected neonatal deaths		34 (6.1%)

TABLE VI. PROBABLE CAUSES OF PREMATURITY AMONG 469 BIRTHS IN THE LYING-IN HOSPITAL (TYSON)

	NUMBER OF CASES	PER CENT	DIED	LIVED
Syphilis	88	18.0	60	28
Toxemia	60	12.0	41	19
Multiple pregnancy	50	10.0	24	26
Premature separation	24	5.0	21	3
Injury to mother	10	2.0	9	1
Placenta previa	9	1.9	7	2
Cardiac	9	1.9	6	3
Polyhydramnios	4	0.8	3	1
Pneumonia	3	0.6	1	2
Nephritis	3	0.6	3	0
Myoma	3	0.6	3	0
Abortion	3	0.6	3	0
Tuberculosis	1	0.2	0	1
Pyelitis	2	0.4	2	0
Acute cold	1	0.2	0	1
Asthma	1	0.2	0	1
Unknown	196	41.8	70	126

Having become "twin-conscious," the author personally observed over 2,000 practically consecutive recent pregnancies in the Preston Retreat for the special purpose of twin management, but even by particular attention to all gravida v and over, and to those who had delivered previous fraternal twins, was able to diagnose manually one set of triplets and only 19 out of 26 pairs of twins before birth, not including one positive false diagnosis in a case of polyhydramnios. When diagnosed, these twin pregnancies were supplied with extra milk and beef, vitamins A, B, D, and G and ferrous sulfate capsules and 8 out of the 14 that were diagnosed in pregnancy were admitted to the ward as "waiting women" at thirty-six weeks. To this simple plan we ascribe a slightly increased average gestation to over thirty-six weeks, avoidance of cesarean section, and protection of the mother by particular care to prevent post-partum hemorrhage as by not too heavy sedation and avoidance of ether. This was, however, offset by bleeding from one lateral placenta previa, one abruptio placentae and one instance of intrapartum hemorrhage due to an acardiacus acephalus attached almost directly to the placenta, causing abruptio placentae. There were five instances of mild and one of severe late gestational toxemia, and no deaths.

In this small series under special attention, 2 out of the 55 infants were stillborn (including the acardiacus, plus one that died from placental necrosis due to toxemia) and five died after birth, one of which was delivered at twenty-six weeks and two at twenty-seven weeks, yielding a corrected total infant mortality of 3 out of 55 infants (5.4 per cent).

SUMMARY AND CONCLUSIONS

1. Maternal, fetal, and neonatal deaths associated with twin and triplet pregnancy have been analyzed from 223,394 total births over sixteen weeks' gestation in Philadelphia from 1931 to 1937 inclusive; and detailed maternal and infant progress from 5 sets of triplets and 305 pairs of twins from the Lying-in, University and Preston Retreat Hospitals has been analyzed.

2. Maternal, stillbirth, and neonatal death rates from twin pregnancies have been shown to be increased roughly about three times over those for single births.

3. The author suggests abdominal tension resulting in renal ischemia or ureteral obstruction as a common factor in both nulliparous "low reserve kidney" and "mild pre-eclampsia" in multiple pregnancy.

4. Quantitative serum and twenty-four-hour urinary excretion of estrogen and prolan should determine whether "low reserve kidney" and many cases of multiple pregnancy toxemia are similar, and distinct from pre-eclampsia.

5. By becoming twin conscious, three-fourths of all multiple pregnancies may be diagnosed manually, and 90 per cent of suspected cases should be diagnosed by x-ray in time to provide dietetic, tonic, and physical support; avoidance of unnecessary cesarean section, and ex-

cess sedation and ether in labor; and hospitalization including preparation for immediate transfusion in all cases, thereby reducing both maternal and fetal accidents by at least one-half.

6. More time up to one hour, and fewer versions are indicated for the second birth, to allow opportunity for the uterus to readjust itself, thereby minimizing the risk of infection and post-partum hemorrhage.

7. Scrupulous management of the third stage of labor, and uterine packing for eight hours in all cases of hemorrhage before or after delivery will prevent many deaths from twin births.

8. Prematurity is the greatest infant hazard, prejudicing the neonatal period more than the natal.

9. Meticulous care, including microscopic examination, in examining the secundines from multiple pregnancy should be obligatory.

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DISCUSSION

DR. BAYARD CARTER, Durham, N. C.—The figures for North Carolina concerning twin pregnancies bear out several features of Dr. Hirst's paper. We find that approximately 40 per cent terminate prematurely. The incidence of toxemia gives roughly a figure of 45 per cent as contrasted with the incidence of about 26 per cent in the ordinary country type of patient who comes to the clinic. The incidence of abruptio placentae and the bleeding syndromes has also been greater than in the single pregnancies.

The answer to the question for the rural population in America depends upon some agency which will take the responsibility of getting these patients into a hospital early. We have asked all social agencies in the state in all cases of patients suspected of an abnormal pregnancy to give us the privilege of seeing these patients early. In that way we were able last year to diagnose for the first time a quintuplet pregnancy by means of x-ray and to avoid fatal delay. This patient was brought to the hospital in very poor condition, with a sudden acute hydramnios and an abruptio placentae.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—It is of considerable importance to differentiate between the pathology associated with uniovular twins and that encountered in binovular pregnancy. There are certain forms of disturbance which are inseparably associated with the one or the other form of multiple pregnancy; for instance, it is possible for one of binovular twins to die in utero without influencing the vitality of the other twin, while it is impossible for one of uniovular twins to be dead for any length of time without causing the death of the other twin. Therefore, in binovular pregnancy one may encounter in one placenta aggressive conditions of the chorionic epithelium, such as hydatidiform mole, or extreme regression of the placenta and necrosis, without either lesion being present in the other placenta. On the other hand, in uniovular pregnancy fetal deformity and monstrosity is very common.

Therefore, in a careful study of the morbidity and mortality of twins it would seem wise to distinguish carefully between the uniovular and the binovular types and classify the pathologic changes under those two headings.

DR. ERWIN O. STRASSMANN, HOUSTON, TEXAS.—There are three established ways of making a diagnosis of multiple pregnancy: first, by observing the fetal heartbeats; second, by physical examination; third, by taking x-ray pictures. Accidentally, we found a fourth way of making a diagnosis of twins when we were taking fetal electrocardiograms during pregnancy.

Up to now, we did not have any objective graphic method of determining whether the fetus is actually alive. Fetal electrocardiography gives graphic evidence of the viability of the fetus in utero. We obtain at the same time in the tracings, taken from the mother, the maternal heart waves and the fetal heart waves which are easily diagnosed on account of their different rhythm, size and direction, the latter corresponding to the position of the fetus.

While taking the tests in the electrocardiographic laboratory, for I did not examine the patients otherwise, a case was sent which I did not know to be twin pregnancy. In the tracings we found two types of fetal waves in addition to the maternal deflections, one being upside down, as we see in vertex presentations, the other upwards, as we see in breech presentations. We were, therefore, in the position to tell on account of the electrocardiogram that there were twins present, that both twins were alive, that one was in a vertex, the other in a breech position. These findings were verified by x-ray picture later.

DR. HIRST (closing).—We should look with suspicion upon every large abdomen in pregnancy, x-ray and possibly electrocardiograph every one, and we should warn small maternity departments to be prepared for any emergency, especially hemorrhage, in these twin cases. In the larger institutions we should have a member of the major staff present at every twin birth if only to restrain the resident obstetrician from doing internal podalic version of the second baby until indicated.

PREVENTION AND TREATMENT OF POSTOPERATIVE THROMBOPHLEBITIS*

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NOTWITHSTANDING a large amount of clinical and experimental study, the etiology and pathogenesis of postoperative thrombophlebitis remains obscure. As long ago as 1898, Welch stated that in any type of thrombosis there were three possible etiologic factors: a local lesion of the intima of the blood vessel, increased coagulability of the blood and relative stasis of the blood stream. It is quite possible that the comparative infrequency of postoperative thrombophlebitis is an indication that all three of the above-mentioned etiologic factors must be present in combination before the lesion develops and, if we were able to eliminate either the local vein lesion or the changes in the blood or the stasis of the blood stream, it should be possible to prevent the formation of the thrombus. From the clinical standpoint thrombophlebitis which occurs as a postoperative complication is an acute vascular accident. It follows a rather definite clinical course with a variable amount of involution and a variable amount of permanent residue. Treatment of this condition, once it has occurred, is not entirely satisfactory and the desirable attack is to prevent it from occurring at all.

Any routine program for the prevention of postoperative thrombophlebitis must take into consideration the fact that this complication is actually rather rare. For example, at The Mayo Clinic during a thirteen-year period, it occurred after only 0.7 per cent of all operations, after 1.6 per cent of all laparotomies and after 2.7 per cent of pelvic operations where laparotomy was performed. Thus, any plan of preventive treatment which is expensive, difficult, or unpleasant for the patient is hardly justified inasmuch as it would have to be carried out on such a large number of patients unnecessarily. Furthermore, the evaluation of any routine procedure can be made only after its use in several thousand consecutive cases. A satisfactory program for prevention has not yet been devised.

LESIONS OF THE INTIMA OF THE VEINS

There is statistical evidence to show that thrombophlebitis occurs more commonly after operations involving the lower part of the abdomen or the pelvic organs, in which there is of necessity some damage to the branches of the internal iliac vein. It also occurs more commonly in patients who have varicose veins of the legs. The incidence is very high after operations in patients who have had a spontaneous attack

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

of thrombophlebitis less than six months before operation. It has been presumed, although never proved, that in severe infections, lesions of the vascular intima may be produced by bacteria or toxins. Thrombophlebitis may occur as a complication of severe infections, such as pneumonia or peritonitis in patients on whom no operation has been performed, and there is an increased incidence of thrombophlebitis in patients whose postoperative convalescence is complicated by such severe infections. The prospect of attack on these various factors in order to prevent the lesion of the intima of the vein is rather poor. It goes without saying that careful surgical technique and a minimum of trauma to tissues during an operation, particularly in the pelvis, should result in a minimum of vein injury. It is also a safe rule to allow six months to elapse before performing an operation on a patient who has had an acute attack of thrombophlebitis of any type except, of course, in surgical emergencies.

STASIS OF THE BLOOD STREAM

Recently Smith and Allen have shown that the venous circulation rate may become definitely slower after major surgical operations. Various attempts have been made to modify this by having patients elevate their limbs and exercise them during the postoperative convalescence. Walters expressed the opinion that the use of thyroid extract reduces the incidence of postoperative thrombosis and embolism. Smith and Allen have shown that it does increase the speed of venous blood flow in these patients. The chief difficulty with the administration of thyroid extract has been to individualize the dosage so that each patient receives enough to produce a physiologic effect and not enough to produce unpleasant or toxic symptoms. The occurrence of relative stasis of the venous blood stream after operation is an argument in favor of keeping patients in bed for the shortest possible period of time during their convalescence. It must also be borne in mind that local venous stasis as well as injury of the veins of the legs may occur when patients are in the lithotomy or Trendelenburg position, when tight binders are placed around the hips and when hard pillows are placed behind the knees during the first few days after operation.

CHANGES IN THE BLOOD

Prevention of postoperative thrombosis by procedures designed to decrease the coagulability of the blood probably offers the best method of attack in the prevention of postoperative thrombophlebitis but work along these lines has just recently been begun. Bancroft and his co-workers have stated that they are able by means of tests of the coagulation factors of the blood to predict which patients have a tendency to thrombosis. Recently Murray and his co-workers have used heparin to prevent postoperative thrombosis. This method is apparently effective but is still rather difficult and not satisfactory as a routine procedure. There seems to be a definitely increased incidence of postoperative thrombosis in patients suffering from blood dyscrasias, particularly polycythemia and anemias of various types. It is recommended that

such conditions be brought under control before operation. In the postoperative period transfusions should be given with care and with careful attention to proper blood grouping. If a patient already has developed a thrombosis, thus indicating a thrombotic tendency, transfusions even with carefully matched blood may be followed by a recurrence of the thrombosis.

OTHER PREDISPOSING FACTORS

Statistical evidence indicates that postoperative venous thrombosis occurs most frequently in the obese (Snell) and in patients suffering from heart disease (Belt) or carcinoma (Welch), so that when operation is considered on such patients, the risk of thrombosis is relatively high. Where time permits, it may be possible to reduce the weight of the obese patient and to treat the heart disease before operation.

TREATMENT

The treatment of postoperative thrombophlebitis after the lesion has occurred must take into consideration the possibility of pulmonary embolism, management during the acute stage of the disease and the prevention of chronic venous insufficiency of the limb. Postoperative thrombophlebitis may occur in many different veins but from the practical clinical standpoint we can restrict this discussion to thrombophlebitis occurring in the lower extremities, since it is rarely found in other locations. Thrombophlebitis occurring in superficial varices is rarely of serious consequence unless it progresses and extends to the larger veins. Thrombophlebitis occurring in the short saphenous vein is fairly common and frequently passes unrecognized. Any pain occurring in the calf of the leg during the postoperative convalescence should indicate a careful examination to exclude the possibility of short saphenous thrombophlebitis. Short saphenous thrombophlebitis is chiefly important because the thrombus is likely to extend to the femoral vein at any time and in doing so the thrombus may be detached and form an embolism. Thrombophlebitis of the long saphenous vein is much less common unless there is a varicosity of this vein. Embolism is rare and subsequent venous insufficiency does not usually occur. Thrombophlebitis of the femoral and iliac veins, the so-called milk leg or phlegmasia alba dolens, usually offers no difficulty in diagnosis and there are certain definite principles which should be observed in its management. Once such a condition becomes manifest, there is a great fear in the minds of most surgeons regarding the likelihood of pulmonary embolism. However, there is clinical and pathologic evidence to show that a thrombus only becomes an embolus soon after it forms. Therefore, the danger of embolism in a patient with thrombophlebitis is on the first day of the formation of the thrombus and usually before the thrombophlebitis can be recognized clinically, or from sudden extension of thrombosis into a larger vein, or from a new episode of thrombosis in another vein.

In a series of 116 consecutive cases of fatal postoperative pulmonary embolism the clinical findings of femoral or iliac thrombophlebitis were present before death in only five cases. In one of these the thrombo-

phlebitis was first evident only a few hours before the embolism occurred. In the other four cases death from embolism occurred on the third, fifth, twenty-first, and twenty-fourth days, respectively, after the clinical onset of a femoral or iliac thrombophlebitis. In each instance necropsy revealed that the thrombus in the affected leg was intact to the level of the bifurcation of the vena cava and the remains of a fresh thrombus were found in the iliac vein of the opposite leg, thus proving that the embolism was the result of a fresh thrombosis. In the majority of cases of postoperative thrombophlebitis, there is only one episode, but there are some cases in which there are frequent episodes affecting different veins at different times. The risk of fatal embolism in a patient who has developed acute femoral or iliac thrombophlebitis of the leg, therefore, is small and usually is dependent on the occurrence of a new episode of thrombosis in a different vein. Thus the prevention of embolism in a patient with the clinical manifestations of acute femoral or iliac thrombophlebitis is a matter of preventing a new thrombus from forming and is not dependent on the treatment directed toward the thrombosis and thrombophlebitis which has already taken place.

Treatment of thrombophlebitis in the acute stage should be directed toward measures to aid the return circulation, as far as possible, and toward measures which will hasten the normal involution of the thrombus and periphlebitis. Adequate elevation will accomplish the former. Adequate external heat will aid the latter.

The liability of patients to develop chronic venous insufficiency of the leg after femoral and iliac thrombophlebitis has not been sufficiently stressed, and prevention of this chronic venous insufficiency is a very important part of treatment. Once the acute stage is over and the patient first assumes the upright position, the factor of orthostatism in retarding the return venous blood flow from the leg and increasing the pressure in the veins of the leg is added to the factor of partial permanent obstruction in the main venous trunk. Although the venous circulation may be entirely adequate for the patient in the horizontal position or in this position with the leg elevated, it is not adequate when he is standing. As the patient resumes normal activity the increased pressure in the veins may produce secondary varices and chronic static edema of the lower leg. More serious complications of chronic venous insufficiency, such as ulceration of the skin, localized indurated cellulitis, and eczema may follow. These complications are probably, to a certain extent, dependent on the inherent ability of the patient's veins to stand strain, and this varies in different individuals. Chronic venous insufficiency is more likely to develop in the obese than in the thin person, and it is also more likely to develop after extensive thrombophlebitis in a leg where venous damage, such as primary varicose veins, already existed. Once a state of chronic venous insufficiency has developed, the treatment of the limb becomes much more difficult. Prevention of such a condition may save the patient long periods of discomfort and disability.

The plan of treatment of postoperative femoral and iliac thrombophlebitis used at the Mayo Clinic is comparatively simple. As soon as

the diagnosis is made the affected leg is elevated to an angle of 30 degrees from the horizontal on a slanting frame or back rest covered with pillows. It is important that the elevation be adequate and that pressure be evenly distributed on the leg. The knee is kept in complete or almost complete extension and the hip in slightly outward rotation. The patient is allowed to move the leg occasionally in changing position. Continuous hot moist packs are applied from the foot to above the groin. The skin is first covered with a thin layer of petrolatum, then with a single layer of gauze. Around this are placed several layers of hot wet blanket material, then two or three hot water bottles and around the entire pack a rubber sheet. Packs are changed often enough to keep them hot but care is taken not to have them hot enough to burn the skin. Opiates may be necessary to control pain during the first twenty-four hours but are rarely needed after this period. The elevation and hot packs are continued until the patient's temperature has been normal for at least three days, until tenderness in the region of the veins—particularly in Scarpa's triangle and the popliteal space—has disappeared and until swelling and edema are gone from the leg below the knee. Slight enlargement of the thigh is disregarded. The hot packs are then discontinued, the leg is lowered to 15 degrees elevation for one or two days and the patient is then allowed up with a proper leg support if his postoperative condition is otherwise satisfactory. In the great majority of cases this is between ten and sixteen days after the onset of the thrombophlebitis. There are two reasons for not prolonging the stay in bed. First, the danger of embolism is past except for the small chance of a new thrombosis and, since postoperative rest in bed with resultant venous stasis is considered one of the factors responsible for postoperative venous thrombosis, prolonged rest in bed after the acute phase of the thrombophlebitis theoretically favors rather than prevents the possibility of a fresh thrombosis and embolism. Second, a long period of rest in bed favors the development of a postphlebitic neurosis (Allen and Brown), it calls attention to a disability of the limb, and it favors muscular weakness and osteoporosis in a limb with impaired circulation. In our experience it is not necessary as a preventive of chronic venous insufficiency if a proper support is worn. It is very important not to discuss the question of thrombosis and embolism with the patient. The fear of embolism and sudden death may become a real phobia and has been the cause of a number of neuroses following thrombophlebitis.

Patients with thrombophlebitis confined to the long or short saphenous veins or to varices may not need leg supports after getting up or may require only a light bandage for a short period. However, it is very important to equip the patient who has passed through the acute stage of a postoperative femoral or iliac thrombophlebitis with an adequate elastic support for his leg and to see that it is properly applied before he gets out of bed for the first time. The support should prevent any swelling of the lower leg and foot after standing or walking. Elastic cloth bandages are uniformly inadequate, rubber and cloth mesh bandages are usually inadequate and most elastic stockings unless very heavy

and carefully made to measure are inadequate. The most satisfactory support is a pure solid rubber bandage 3 inches by 15 feet. It can be removed and reapplied at any time if the tension is not right. It is heavy enough to prevent any postphlebitic edema if properly applied and its wearing qualities are excellent. Its disadvantages are that it may produce discomfort from heat, particularly in the summer, that the patient must learn to apply it, that some patients, chiefly women, object to its appearance and that some skins are sensitive to rubber. Second choice in supports is a heavy elastic stocking made carefully from measurements.

The support should be applied from toes to knee with only a small portion of the heel exposed and this should be covered by the heel of the shoe. In using the rubber bandage a long white cotton stocking is put on the leg first. It is difficult or impossible to apply a support, either bandage or elastic stocking, to the knee and thigh that will not slip and will not irritate the popliteal region when the patient walks. Some swelling of the thigh may occur when the patient is active but usually this disappears spontaneously in time and serious complications of venous insufficiency rarely occur in the thigh. The patient should be instructed in the application of the bandage. It should be wrapped snugly but not under tension. It should be applied in the morning before he gets out of bed, removed and rewrapped at noon and at about 6 P.M., and removed again at bedtime. For one or two months the patient should sleep with his leg on a pillow. With the bandage on, ordinary activity is permitted except that standing without walking should be minimized. When sitting, the feet should be elevated on a stool if possible. Exercises with the leg elevated are advisable. After three months the bandage is left off for a half day and, if no swelling of the leg appears, for longer periods. If the swelling is minimal, a lighter bandage may be worn for a longer period of time. If it is definite, the heavy bandage should be continued for one or two more months and another trial made without it.

The results of treatment according to the plan mentioned above, in 54 carefully studied cases of acute postoperative femoral and iliac thrombophlebitis were as follows: Pain became minimal within twenty-four hours after treatment started and was completely relieved within five days from the onset of phlebitis in 66 per cent of the cases and within ten days in 91 per cent of the cases. Fever in cases uncomplicated by other infections disappeared within one week from the onset of phlebitis in 81 per cent of the cases and within twelve days in all cases. Swelling of the leg below the knee and edema had disappeared within fourteen days from the onset in 81 per cent of the cases and within eighteen days in all cases. Tenderness in Scarpa's triangle and the popliteal space was gone within sixteen days in all cases. Eighty-one per cent of the patients were allowed up from the tenth to the sixteenth day after the onset, depending on disappearance of symptoms, and all were up within twenty-four days. In over half of the patients the pain disappeared in two to four days, the fever in five to seven days, the swelling in ten to fourteen days, the tenderness in ten to fourteen

days, and they were up in ten to fifteen days from the time of onset. It has not been shown that leeches, roentgen therapy, diuretics or injections of sodium thiosulfate added to simple, but adequate, heat and elevation have shortened the acute stage or hastened the involution of postoperative femoral and iliac thrombophlebitis.

Of our 54 patients, only one died of pulmonary embolism. This occurred twenty-eight days after the onset of a left iliac thrombophlebitis. At necropsy the thrombus in the left iliac vein was found to be intact and well organized, and the remains of a fresh thrombus (unrecognized clinically) were found in the right iliac vein. This patient had been kept in bed an unusually long time, twenty-four days after the onset of the left iliac thrombophlebitis, because of other postoperative complications but had been up for four days when death occurred. Three patients of the 54 died subsequently of the disease for which operation had been performed (carcinoma). The remaining 50 have been followed by subsequent examination or letter for from three to eight years following their thrombophlebitis. Not all were treated with the same type of leg supports. The ultimate results from the standpoint of chronic venous insufficiency are as follows:

Thirty-five patients were equipped with the heavy rubber leg bandages. Twenty-seven of these (77 per cent) were able to discard the bandage within two to twelve months after the onset of the thrombophlebitis and subsequently did not develop edema, varicose veins, ulcers, eczema, or pain on walking. Three patients developed mild to moderate static edema of the leg after discarding the bandage but no other signs of venous insufficiency. Two patients subsequently developed chronic edema and definite varicose veins with some pain in the leg after discontinuing the bandage. (One of these stopped wearing the bandage after six weeks, against advice.) Three patients had to continue to wear the bandage and are still doing so, as going without it produces rather marked pain and swelling of the leg. These represent severe degrees of chronic obstruction of the iliac vein. None of this group has developed ulcers, cellulitis or stasis eczema. Of 3 patients who were equipped with elastic stockings instead of rubber bandages one was finally able to discard the stocking without further trouble. Two developed chronic edema in spite of the support. Of 12 patients given cloth elastic bandages, 4 ultimately discarded them without further trouble. Five developed chronic edema. Two developed edema, pain and varices and subsequently were given rubber bandages which they are still wearing and one patient developed severe pain, eczema, and a chronic ulcer of the leg.

For comparison a study was made of 50 patients who were seen at the Mayo Clinic during the same five-year period and who had had a postoperative femoral or iliac thrombophlebitis less than five years previously. This group of patients had had various types of treatment. Many of them had been kept in bed for periods of several months after the acute stage of the thrombophlebitis but none of them had worn heavy rubber bandages or adequate supports. Some had had no sup-

ports at all. Only 5 patients in this group (10 per cent) had no trouble with the affected leg, 11 (22 per cent) had mild swelling and pain after walking, 15 (30 per cent) had rather marked edema and had developed definite secondary varicose veins, and 19 (38 per cent) developed not only edema, pain, and varicose veins, but also ulcers and cellulitis. Six patients out of the 50 in this group had developed a definite postphlebitic neurosis and 5 of these had been kept in bed for more than two months after the acute stage of the phlebitis.

From a more detailed comparison of this group of patients with those who were given adequate support, we feel that the prevention of chronic venous insufficiency following postoperative femoral and iliac thrombophlebitis with its more serious sequelae of ulceration and cellulitis depends, not on the length of time that the patient is kept in bed following the acute stage, but on the adequacy of the supporting bandage which he wears after resumption of orthostatic activity.

SUMMARY

No satisfactory routine procedure has been devised for the prevention of postoperative thrombophlebitis. Certain measures have been discussed which will help to minimize the three essential factors of local vein injury, slowing of venous blood flow and alteration in the coagulability of the blood.

Postoperative thrombophlebitis may be successfully treated in the acute stage by adequate elevation of the limb and the use of extensive hot wet packs locally. It is advisable to get the patient up as soon as the temperature has been normal for three days, swelling below the knee has subsided and local tenderness in the involved veins has disappeared. As soon as the patient is out of bed it is necessary to equip him with an adequate leg support and for this a heavy pure rubber bandage is recommended. The bandage can usually be discarded in from three to twelve months without the subsequent appearance of any signs or symptoms of chronic venous insufficiency. Once the clinical picture of acute postoperative femoral or iliac thrombophlebitis has appeared, the danger of fatal pulmonary embolism is small.

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DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—Trauma and infection, particularly the latter, are in my opinion the most important factors in the production of thrombophlebitis. For this reason in doing hysterectomies we endeavor to limit as much as possible the crushing of tissues which are to be left in the pelvis after operation. All total hysterectomies are drained vaginally to reduce the danger of infection of clots present in vessels severed at operation.

In my experience there has quite frequently been evidence of thrombophlebitis before the loosening of pulmonary embolus. Furthermore, we are continually on the look-out for evidence of small emboli which produce pleuritic pain, possibly some cough and expectoration but none of the dramatic symptoms seen in large pulmonary emboli. These small emboli may precede the larger ones by several days, and when noted should indicate the maximum immobilization of the patient until sufficient time has elapsed for the thrombus to become well organized, which may, in our opinion, be about three weeks. We do not allow the patients to sit up in bed, turn over, or use the bed pan without assistance. I believe they would be safer still if strapped on a Bradford frame and we have done this occasionally. We have noticed frequently in cases of thrombophlebitis that a rise in pulse rate out of proportion to the rise in temperature frequently precedes the clinical signs of the condition.

We do not share Dr. Counseller's fear of creating a neurosis by telling the patient with thrombophlebitis of the possible dangers of pulmonary embolism. We feel that to get the cooperation which is so essential in the management of this condition it is necessary to tell most patients exactly what the consequence of failure to cooperate on their part may be.

The following statistics show that in a period of ten years we have had 21 cases of thrombophlebitis among 2,785 operations, an incidence of 0.67 per cent. These were all pelvic laparotomies. There were 3 deaths, a mortality of 0.107 per cent.

DR. WILLIAM T. BLACK, MEMPHIS, TENN.—At the John Gaston Hospital, Memphis, in a series of 4,205 cases in the Gynecological Service 7 cases of thrombophlebitis were reported. There were 3 deaths due to an embolus. One of these was a cardiac embolus, the other two pulmonary.

No doubt cases of thrombophlebitis of mild degree occur following pelvic operations, which are never diagnosed as such. Mild unexplained pelvic infections with a slight rise in temperature, pain, and tenderness are often due to thrombophlebitis.

Thrombophlebitis is more likely to occur in a dehydrated, anemic and septic patient. Therefore, fluids and blood transfusions are indicated preoperatively and postoperatively. Keeping the patient in one position too long during and after an operation predisposes to a thrombus formation. Those with a previous history of thrombophlebitis should be handled with great care during an operation for fear of an embolus. Gentleness in technique is good prophylactic treatment.

If the tests could be carried out routinely as recommended by Bancroft and his co-workers, no doubt thrombophlebitis could often be prevented. I have used thyroid extract, as advised by Walters, but have been unable to form definite conclusions. Sodium thiosulphate may be used. Heparin promises more than any other agent as demonstrated by the splendid work of Murray and Best. The newer preparation of heparin is said to be free of any toxic property and is of course a splendid anticoagulant.

DR. W. WAYNE BABCOCK, PHILADELPHIA, PA.—We have all seen the pale swollen leg that not a few patients carry throughout the remainder of their lives. While the involvement of superficial veins alone may later give rise to varicosities and ulcer, the condition is less serious and may be taken care of by sclerosing injections. It is involvement of both the superficial and deep veins that is particularly harmful.

I wish to emphasize the danger of traumatizing thrombosed veins during the acute stage. I recall a physician who died within a few minutes after his leg was massaged for severe pain associated with the onset of a thrombophlebitis.

At times the thrombus becomes infected and an abscess forms. As ligation of a proximal vein was advised for thrombosis of the lateral sinus, thirty years ago I ligated the long saphenous for a severe phlebitis of the leg to prevent an extension of the process. A fatal shower of emboli followed. A similar procedure done by a colleague was also fatal. On the other hand, I do not recall a fatality where the surgeon had waited for the abscess to point and had merely incised. We now believe that ligation or removal of the thrombus early in any case of septic thrombophlebitis is very dangerous.

DR. ALBERT MATHIEU, PORTLAND, OREGON.—If an abdominal binder is tight enough to do any good, it is harmful; and if it is not tight, it is worthless. I am very much opposed to the binder that binds the patient like a plaster of Paris cast, because some of these cases of thrombophlebitis have originated in veins in the abdominal wall. I highly disapprove of pillows under the patient's knees and hospital beds which buckle up under the patient's knees. By these means the patient's circulation in the legs is impaired. The patient rather should be encouraged to move the legs frequently. I have seen one death following vaginal hysterectomy with the site of the thrombus in the veins beneath the gastrocnemius muscle.

DR. F. S. WETHERELL, SYRACUSE, N. Y.—We have for some years followed a method which seems to have cut down what previously was an incidence of thrombophlebitis similar to that reported by Dr. Counseller. The method is simple and undoubtedly many of you use it, and consists simply in the inhalation of CO_2-oxygen every two hours for three minutes. It is impossible to breathe deeply and rapidly for a greater length of time. I continue that regime for two or three days, or longer, if the patient seems to be a potential candidate for thrombophlebitis. It is used routinely in every case, whether pelvic or abdominal.

I think the members of this Association have here a problem which they might well work out together.

DR. WILLIAM A. COVENTRY, DULUTH, MINN.—In my own town there are two surgeons who in order to prevent thrombophlebitis write out so many orders that the patient is exhausted if the orders are properly carried out. I, myself, have for the last five years simply had the patients move about in bed on their own power. This exercise promotes circulation in the deep veins.

PROFESSOR CHARLES BURGER, BUDAPEST, HUNGARY.—I wish to call your attention to a therapy that in the very beginning, or if the lesion has not progressed too far, may influence the course favorably and lessen the pain; that is x-ray therapy. The application of leeches in the inguinal region may, according to our experience, be favorable in diminishing the pain, and one can make use of this when x-ray is not available.

DR. V. S. COUNSELLER (closing).—I am impressed with the fact that embolism and phlebitis occur more frequently in spring than in the fall. This observation has been made previously at the University of Illinois. In June and July of this year we have had more rain and have seen more phlebitis than in the same months for many years in Minnesota.

The late Dr. George Brown instituted at our clinic a method of management of postoperative thrombophlebitis and of embolism. As soon as such a condition is encountered the Vascular Service is notified. Extreme care has been taken to teach assistants how to care for such diseases and a conference with the patient is held before he leaves the hospital in order to instruct him as to further treatment. A follow-up system has also been instituted.

RECENT DEVELOPMENTS IN DIAGNOSIS AND TREATMENT OF HYDATIDIFORM MOLE AND CHORIOEPITHELIOMA*

ALBERT MATHIEU, M.D., F.A.C.S., PORTLAND, ORE.

WHEN the literature of the last few years is reviewed and contrasted with former writings, it is evident that there has been intelligent activity and noteworthy advances as regards hydatidiform mole and chorioepithelioma. Up to 1930 the diagnosis of hydatidiform mole rested on the demonstration of hydatid vesicles, and the diagnosis of chorioepithelioma was rarely made until metastases had occurred. Since 1929, when Zondek discovered that gonadotropic hormone was present in the urine of patients with hydatidiform mole, and was greatly increased in amount over that of normal pregnancy, and since 1930, when this same discovery was made with relation to chorioepithelioma, diagnosis, treatment, and prognosis of these diseases have changed to a remarkable extent. An analysis of the extensive papers written prior to 1930, including about 1500 cases of chorioepithelioma and probably ten times as many moles, shows that the mortality rate of mole was approximately 12 per cent and that of chorioepithelioma 60 per cent. A review of the world's literature for the last three years, involving 576 cases of mole and 266 of chorioepithelioma, shows the mortality rate now to be approximately 2 per cent and 10 per cent, respectively.

At present it seems that diagnostic criteria are adequate but that diagnostic acumen is lacking, and that maximum results in treatment are not being obtained because of inertia on the part of the clinician or nonacceptance of the newer criteria. Because of insufficient experience no man can speak authoritatively on these diseases, but a review of contemporary literature enables us to assemble the important factors responsible for improved diagnosis and reduced mortality.

The most important single development in diagnosis and treatment is the test for chorionic gonadotropic hormone. It is generally accepted that this test is positive and that the amount of hormone is increased in mole and chorioepithelioma.

Recently there have been reports of positive pregnancy tests with the contents of lutein cysts, with fluid aspirated from the chest, with fluid from hydroceles, and with various tissues of the body. When one considers that patients harboring mole or chorioepithelioma have great quantities of chorionic gonadotropic hormone in the blood, it is obvious that this hormone will be present in all fluids and tissues of the body.

While the cerebrospinal fluid gives a negative test in normal pregnancy, it gives a positive test in mole and chorioepithelioma. Smith

*Presented at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

and Smith found that when chorionic cells become neoplastic they do not contain estrin in amounts comparable with those found in normal placentas. May not this lack of estrin in pathologic chorionic cells be the factor accounting for the excessive amount of gonadotropic hormone!

Although all authorities agree on the value of the biologic pregnancy test in the diagnosis of mole and chorioepithelioma, it should be noted that there have been many misconceptions of the test—laboratory errors (2 per cent), too much reliance on a single test, and clinical and pathologic judgment at variance with the test. The pregnancy test is always positive only if there is living chorionic tissue present or when the stored hormone has not been completely absorbed.

The qualitative test is not sufficient since the increasing amount of hormone associated with these diseases is detectable only by a quantitative assay. Nevertheless, one should not overlook the fact that at about the sixtieth day of normal pregnancy there is an enormous amount of the hormone. In the pursuit of mole and chorioepithelioma by means of biologic pregnancy tests, one must be certain that normal pregnancy is not present.

Quantitative estimations of the hormone by some other method than that of Aschheim and Zondek have been attempted. Schoeneck determined the minimal amounts of urine, at various stages of normal pregnancy, required to produce positive Friedman reactions. In the Brindeau-Hinglais method curves showing the hormone content of the serum were developed by injecting measured quantities of the patient's blood serum into rabbits.

Quantitative tests are at times impractical, inexpedient, or even impossible. When only qualitative tests are used, one must be aware of the following facts: (1) the test is positive in the presence of living chorionic tissue, which includes normal pregnancy; (2) the test is also positive in hydatidiform mole, chorioepithelioma, or metastases of either disease; (3) the test may be negative in missed molar abortion; (4) the test may be positive for six weeks following the passage of a mole because of stored hormone in the body; (5) if a test is positive two months after the passage of a mole, and normal pregnancy has been excluded, it is likely that living molar tissue is still present or chorioepithelioma has developed; (6) in the presence of lutein cysts after all living chorionic tissue has been removed, the test will be positive until these cysts regress because the hormone is stored in them; (7) a positive test one month after the removal of a chorioepithelioma is strong evidence of metastasis; (8) the spinal fluid gives a negative test in normal pregnancy and a positive test in mole or chorioepithelioma; (9) absolute reliance should not be placed on one test, and in questionable cases the test should be checked and rechecked; (10) the test should be used in all questionable conditions where the element of chorioepithelioma might exist; and (11) the biologic test should overrule contrary clinical and pathologic findings. During a period of a week or so following mole, there might exist a

nidus of chorioepithelioma which is too small to produce a sufficient quantity of hormone to be detectable by methods now extant. Although such a nidus is a rarity, it probably explains those few cases reported in which there was a negative test at some period during the transition of mole into chorioepithelioma. If such a nidus exists, it will not be long before it grows sufficiently to give a positive test, or, the test will be positive before the disease gets beyond easy clinical control.

Little progress seems to have been made toward the solving of the etiologic puzzle involved in these conditions, nor do we know all we should concerning their interrelated pathology. There just begins to creep into the literature reference to the fact that interested pathologists are making apparently successful attempts to differentiate between the benign mole and the mole with malignant potentialities. Hertig's report on a series of paraffin blocks, slides, and follow-up records of over 100 cases of mole is a challenge to pathologists to organize their material and study it meticulously, not only with the idea of attempting to establish malignant potentialities in moles, but also to detect the early or small focus of chorioepithelioma. If this is to be accomplished, it can be done only by correlated study of a mass of material.

When the diagnosis of mole is uncertain the patient should be treated conservatively, but once the diagnosis is certain, it is probably best to empty the uterus at once through the vagina. An important part of the treatment of mole is watchfulness for the advent or presence of chorioepithelioma. Evidence indicates that there are many cases of simultaneous occurrence of these two diseases. In the follow-up treatment there should be repeated biologic pregnancy tests which, when correlated with the clinical findings, will show the presence or absence of chorioepithelioma. The greatest pitfalls in the follow-up treatment of mole are lack of knowledge that chorioepithelioma may ensue and the misconception of the biologic pregnancy test.

Early diagnosis and immediate hysterectomy offer the best chance of cure of chorioepithelioma. Total hysterectomy or subtotal hysterectomy should depend on whether or not the cervix is involved or otherwise diseased. It is generally conceded that in most cases the removal of the primary growth results in retrogression of metastases. Extensive metastases need not delay the operation.

The presence of lutein cysts in conjunction with these diseases is a very interesting biologic phenomenon. These cysts appear to be sequential rather than the cause of mole or chorioepithelioma, and since they are apparently the result of constant bombardment of increased chorionic gonadotropic hormone, the longer the mole or chorioepithelioma exists the larger the cysts will become. Fewer lutein cysts will be reported in the future, for we have every reason to believe that ultimately diagnosis will be made before they are formed. In my cases of chorioepithelioma following mole, in which

diagnosis was made early and hysterectomy done, there were no lutein cysts visible in any of the ovaries. Torsion is the only indication for removal of lutein cysts because they regress when the primary focus is removed. The ovaries should not be removed unless they are definitely involved by the disease. Only a few surgeons have had the courage of their convictions and the pioneering spirit to remove the uterus and leave the ovaries in young women. These few have been paid for their courage and with no loss to the women.

Reports of treatment by roentgen ray and radium are beginning to appear. Some authors feel that irradiation is of value when the patient has an inoperable growth or when the surgical risk is great. Others think that irradiation should be used in addition to operation, either before or after, and that when it is employed, the dose should be as large as the patient can tolerate. It is contended that chorioepithelioma and mole are extremely radiosensitive because of their embryologic cell type. While treatment by irradiation seems to be well founded theoretically, and while a few cures have been reported, the majority of the reports are not very promising.

There is a strong feeling against curettage in the diagnosis of chorioepithelioma as it is liable to disseminate the lesion or cause perforation of the uterus, and because it may be extremely misleading and result in mismanagement of the case where the lesion is buried deep in the myometrium and inaccessible to the curette. A great deal of this argument can be applied to hysterotomy as treatment of this lesion. Naïve dependence on curettage or hysterotomy may result in tragic sequelae.

Since hysterectomy is the operation that cures, it seems best that we abandon curettage and not take up hysterotomy. While abandonment of curettage might seem extremely radical, when we estimate the rare good it does, the harm it does, and what better information we can get through biologic pregnancy tests, it seems advisable. Just as in acute appendicitis and ectopic pregnancy, all patients should be operated upon as soon as the diagnosis is made in order to obtain the best results and serve the common good. In a few cases it appears that the uterus was removed needlessly, but these cases are rarities and need not influence our conduct. While occasionally there is injected an argument by a pathologist that certain chorioepitheliomas might have regressed and hysterectomy have been avoided, the report of regression, which is a rarity, should not dominate the situation. Waiting for regression of the chorioepitheliomatous lesion surely does not constitute one of the factors responsible for the lowered mortality rate obtained at the present time. A study of the recent literature almost invariably shows that the patient was cured when the disease was diagnosed early and hysterectomy performed immediately, and that the deaths were recorded among the group in which diagnosis and treatment were delayed or in which the disease was of long standing. In 1928 Ewing said he had "been unable to find any record

of operative cure of choriocarcinoma." Recently cures of such cases have been reported, and two of my patients who had choriocarcinoma were cured.

There is a suggestion that some lytic substance might possibly be evolved as a cure. This is based on the fact that approximately 80 per cent of pregnant women have living chorionic cells in their circulation, and that after delivery a lytic substance is present in their blood which destroys the chorionic tissue, that is, serum of normal women during pregnancy is able to destroy migratory chorionic cells, while serum from women with chorioepithelioma does not seem to possess this lytic action. The lack of this substance is held to be responsible for the almost 100 per cent mortality in teratomatous chorioepithelioma of the ovary and the testicle. It has been recommended that selected patients with hopeless choriepithelioma be treated by intravenous administration of large doses of serum from the pregnant human female, and if the reaction is favorable that serum from one of the lower animals, such as the mare, be investigated.

Notwithstanding the fact that recent advances have done much toward the perfection of diagnosis and treatment, there remains much to be done. Careless and fragmentary reporting of cases must be avoided because more harm than good is done by slipshod reporting of paradoxical cases replete with inconclusive evidence. Editors should refuse papers on such a controversial subject unless these papers show all the earmarks of thorough, scientific study and honesty of purpose. Furthermore, loose concepts must be abolished; more exact knowledge and better interpretation of the tests for gonadotropic hormone must be had; and a technic better than is at present extant is needed so that the most minute amount of living chorionic tissue can be revealed. And it is to be hoped that ultimately criteria will be formulated that will establish potential malignancy of mole, thereby enabling us to prophesy the advent or to determine the existence of chorioepithelioma. Whether this will be done by the pathologic investigator or by the endocrinologic investigator remains to be seen. A wide exchange of material under the guidance of an unified group of competent pathologists might be the solution. The highest percentage of cures will be gotten when there is judicious correlation of clinical history, verified histologic examinations, and intelligent interpretations of the biologic pregnancy tests. It would appear if modern criteria are used, early diagnosis made, and early operative treatment instituted that the woman with chorioepithelioma will have approximately a 95 per cent chance to get well and keep her ovaries.

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DISCUSSION

DR. T. L. MONTGOMERY, Philadelphia, Pa.—Some few years ago, after making a study of our cases at the Jefferson, I presented a paper before the College of Physicians of Philadelphia on the subject "Aggressive Phases of the Chorionic Epithelium." Upon re-reading the observations of that paper, I find no reason to change the opinions expressed therein and desire to present them to you.

1. A study of the life cycle of the chorionic epithelium reveals in the course of pregnancy normal periods of aggression and regression.

2. Abnormal stimulus at fertilization may manifest itself either in the form of early regression with ultimate necrosis of the placenta and intrauterine death of the fetus, or in aggression eventuating in hydatidiform mole or chorioepithelioma.

3. The presence in one side of a binovular pregnancy of premature regression, or of aggression and hydatidiform mole, while the neighboring embryo is normal, indicates that these phenomena arise upon fertilization of the ovum and are inherently hereditary in nature.

4. The aggressiveness of the trophoblastic elements varies widely in intensity from the mild forms of hydatidiform mole to the extremely malignant types of chorioepithelioma. It appears unnecessary and impossible to "pigeonhole" each pathologic specimen in the diagnostic classifications such as have been suggested by Ewing and others.

5. Through the production of lytic substances nature has provided in normal pregnancy for the limitation of chorionic growth to the wall of the uterus and the destruction ultimately of those bits of syncytium that wander through the mother's circulation.

6. Even in hydatidiform mole and chorioepithelioma of pregnancy, some attempt is made in this same direction by these obscure or "x" factors of maternal resistance, and if the main mass of tissue is removed mechanically, oftentimes the outlying deposits will be taken care of by these lytic processes.

In the light of such observations it would appear that we have two factors which must be given attention in our treatment of the aggressive phases of the chorionic growth: (1) the innate growth stimulus which occurs at fertilization; and (2) a maternal resistance factor (x) which develops during the course of the growth.

The presence of a large amount of gonadotropic-like hormone is evidence of ascendancy in growth of the chorionic epithelium. In normal pregnancy this epithelial formation which is at first aggressive, later undergoes regression and is ultimately cast off as the placenta and membrane, upon which the maternal factors of lysis quickly assume the ascendancy and destroy the syncytial strands which remain at the placental site.

In hydatidiform mole and chorioepithelioma natural regression does not take place, and if the system is not rid of the nefarious and parasitic material, the host will be destroyed. How the host will take care of the outlying strands of tissue and the migrant cells after removal of the primary mass becomes the important consideration in formulating a prognosis. Ultimately we will find a way to increase lytic substance in the maternal system and perhaps raise it to a level which will be effective in chorioepithelioma.

DR. S. A. COSGROVE, JERSEY CITY, N. J.—It is very evident that the single factor responsible for the change from the almost hopeless picture of a few decades ago to the decidedly good prognostic outlook of the present is the application and evaluation of the repeated quantitative estimation of gonadotropic hormone. Therefore it seems to me that we should not tolerate a condition which he describes in the statement that quantitative tests of this sort are at times "impractical, inexpedient or even impossible." In a matter of so great moment the profession should be able to devise means whereby such quantitative tests might be made available to sufferers from these diseases.

The situation could be briefly summed up, except for a small percentage of laboratory errors, in the following way:

1. When, consistent with clinical history, a supposed pregnancy shows by repeated quantitative hormonal tests a much higher titer of hormone values than is normal in pregnancy, hydatidiform mole or chorioepithelioma may be diagnosed with high probability.

2. When, following the extrusion of a hydatidiform mole, persistent or reappearing hormonal tests in exceedingly high titer show a progressive increase, then chorioepithelioma should be unhesitatingly diagnosed and operative interference promptly instituted.

I would be inclined to amend only one statement made by Dr. Mathieu in his discussion of the significance of these tests. He says, "The biologic test should overrule contrary clinical and pathological findings." I would prefer the statement: "The repeated *positive* biologic test should overrule contrary clinical and pathological findings." But if negative biologic tests are not consistent with suggestive clinical findings, then the result of biologic tests should not lull one into a false sense of security, as has been so significantly shown by a case reported by Schumann.

Too great emphasis cannot be placed on Dr. Mathieu's insistence on three most important principles:

1. The prompt operative treatment of mole and persistent biologic follow-up after its extrusion.
2. Prompt hysterectomy in every case where the existence of chorioepithelioma is even highly probable. I believe total hysterectomy better in all these cases, lest occasional involvement of the cervix be overlooked.
3. The conservation of the ovaries in those cases where chorioepithelioma is diagnosed early, and the ovaries are not definitely diseased.

DR. F. J. SCHOENECK, SYRACUSE, N. Y.—Dr. Mathieu mentioned a quantitative Friedman test in connection with the diagnosis of hydatidiform mole. We have developed a comparatively simple procedure which may be carried out in any laboratory that is doing Friedman tests.

We have established the minimal amounts of urine that will give positive reactions during the early weeks of pregnancy. In general, positive reactions may be obtained between the sixth and twelfth weeks of pregnancy with amounts varying from 1 c.c. to 0.1 c.c. As a rule the smallest amounts are necessary between the eighth and eleventh weeks.

With such normals established, we can easily determine specimens in which there are greater amounts of hormone present. This is done by injecting the test animals with 0.025 c.c., 0.0125 c.c., etc., of urine. In actively growing moles we have obtained positive reactions with as little as 0.0063 c.c. The only requisite is additional test animals. Inasmuch as we laparotomize the rabbits and use them again and again, the expense of the test is not too great.

There are several cautions that must be observed in the use of such a quantitative test. Aside from hydatidiform mole, we have found at least two other conditions in which more hormone is excreted than in the instance of normal pregnancy, notably excessive vomiting of pregnancy and multiple pregnancy. Thus, we can imagine a case of multiple gestation associated with excessive vomiting and threatened abortion, giving not only a perfect clinical picture of hydatidiform mole, but being confirmed by laboratory findings. Such a case erroneously diagnosed as mole and treated as such by cleaning out the uterus might be, to say the least, embarrassing.

Also, there are certain types of hydatidiform mole that in our experience have not been associated with an excessive excretion of hormone. We had two instances in which there was actually less hormone than would be expected for normal pregnancy. Neither of these moles on expulsion showed the typical pathologic picture. According to our interpretation, they were undoubtedly undergoing degeneration, presenting a solid mass with only very few vesicles.

A final point: While it is necessary to employ the quantitative test to differentiate hydatidiform mole from normal pregnancy, when we are dealing with a possible chorioepithelioma, the ordinary qualitative test is quite sufficient. While the quantitative test is interesting scientifically and may be of importance from a prognostic viewpoint, the ordinary test will suffice for diagnosis.

DR. LOUIS E. PHANEUF, BOSTON, MASS.—I have had a personal experience with 9 hydatidiform moles and 4 chorioepitheliomas. These cases were published in the *New England Journal of Medicine*, 217: 270, 1938. Dr. Arthur T. Hertig, pathologist at the Boston Lying-In Hospital, listed in the discussion of these cases certain observations which are helpful in settling the question of malignancy. He regarded certain moles as benign because of the following general histologic picture: 1. Normal chorionic epithelium. 2. Slight, undoubted benign hyperplasia without mitoses or anaplasia. 3. Moderate to marked benign hyperplasia with occasional anaplastic cells, that is, those of increased size with enlarged, irregular hyper-

chromatic and darkly staining nuclei. Hertig based the diagnosis of "potentially malignant," "probably malignant," or "malignant" on one or more of the following features: 1. Invasion of villous stroma by relatively undifferentiated chorioepithelial elements. 2. Moderate to marked anaplasia of the epithelium, either with or without mitotic activity. 3. Tissue culture-like growth of detached chorioepithelial elements, usually in fairly large masses and growing upon the surface of a blood clot.

I prefer panhysterectomy with double salpingo-oophorectomy in chorioepithelioma because in the presence of this highly malignant new growth, the chances of cure are enhanced by removing the entire pelvic organs. Dr. Mathieu is not in accord with this since he is of the opinion that the lutein cysts will regress when the primary focus, the uterus, is removed.

DR. HENRY SCHMITZ, CHICAGO, ILL.—About eight years ago I reported to this Association observations on eight cases. Out of seven primary choriocarcinomas, two were treated with radium and roentgen rays. Both survived the five-year period, one for ten years, when she succumbed to a heart disease; the other one was treated twenty-one years ago and is still living today. Three patients had a panhysterectomy with postoperative roentgen irradiation. One patient had only a hysterectomy. The absolute cure in the seven primary cases was 85.7 per cent. The mortality in one case resulted from late diagnosis and infection. The recurrent choriocarcinomas did not react to any kind of treatment.

The good end results of treatment depend on early diagnosis. The Aschheim-Zondek test has enabled us to render an early diagnosis. Recently we had a case of hydatidiform mole in which the Aschheim-Zondek test was obtained with 1/250th of a cubic centimeter of urine. The patient was curetted and a twin pregnancy was found. The chorioepithelioma was entirely confined to one of the pregnancies.

DR. EMIL NOVAK, BALTIMORE, MD.—It should be emphasized that we cannot make a final diagnosis with these biologic methods. The final diagnosis in chorioepithelioma must be on the basis of a pathology. Many of the biologic characteristics which Dr. Mathieu has described apply equally to benign hydatidiform mole and malignant chorioepithelioma.

I am impelled to emphasize this point because of Dr. Mathieu's statement that he thinks that with the employment of these biologic methods a patient with chorioepithelioma will have a 95 per cent better chance of cure than formerly. That is a rather startling statement. First, chorioepithelioma is a very malignant tumor, in the great majority of cases. Second, it is a very rare tumor. In our laboratory at the Johns Hopkins Hospital we have specimens of about 48,000 cases and among them we have not had more than about 8 or 9 chorioepitheliomas. Some years ago Dr. Symmers of New York reported that in some 32,000 autopsies he had never seen a chorioepithelioma. We should be inclined to lean backward in reaching such a diagnosis.

Sometimes pathologic diagnosis is quite simple, in other cases difficult. In a borderline case it is difficult to say whether we are dealing with a benign hydatidiform mole, with marked trophoblastic proliferation or with a real chorioepithelioma. When we get large masses of trophoblast growing in bulk, with few or no villi, and destroying the uterine muscle, and with abundant evidence of anaplastic activity, there is little difficulty about the diagnosis. But in a perfectly benign hydatidiform mole if the sections are from the uterine wall, where the mole is getting plenty of blood supply, and not from the vesicles in the uterine cavity, we may be confused by the large masses of trophoblastic tissue, which nevertheless is not evidence of malignancy. I believe that many more mistakes of diagnosis are made in this particular field than in any other. Even normal pregnancy has often been mistaken for chorioepithelioma because of the frequent presence of numerous trophoblastic cells deep in the musculature beneath the implantation area, though this is entirely normal.

In view of what we know as to the malignant course of genuine chorioepithelioma, and its frequently very early metastases, it seems almost incredible to me to expect a

reduction of mortality to only 5 per cent as Dr. Mathieu has suggested, no matter how conscientiously and intelligently one may apply the biologic methods which he has discussed.

DR. JOE V. MEIGS, BOSTON, MASS.—Lutein cysts, in my experience, should not be left behind if they are large. We have had two such cases in recent years. In one the cysts were the size of oranges and were bleeding. The patient was in severe shock. The other had a cyst the size of a child's head on each side. I doubt the regression of any of these cysts.

One fact has not been stressed today, which I think is probably true, that following a normal pregnancy one is more likely to have a choriocarcinoma and after hydatidiform mole a chorioadenoma that is less malignant.

It is essential to remove the cervix in chorioepithelioma. One of our patients developed a tumor five years after operation. There is a chain of lymphatics running down into the cervix from the body of the uterus.

Placental polyps are confusing because months or even a year after delivery a piece of placenta left behind can cause bleeding and microscopic differentiation is often very difficult. It should be recognized that there may be placenta left in utero for a long time.

DR. JAMES K. QUIGLEY, ROCHESTER, N. Y.—I wish to relate very briefly two interesting phenomena that I saw in March in connection with a hydatid mole. The first was an extreme degree of what we would ordinarily call a toxemia, with hypertension, albuminuria and extreme jaundice so that the patient almost died from the toxic state before she expelled the mole. Second, she developed a lutein ovarian cyst the size of a child's head. After the expulsion of the mole there was a diminishing quantitative Friedman test, but the cyst kept increasing in size. I removed this cyst but left 2 or 3 small lutein cysts of the opposite side.

DR. MATHIEU (closing).—Regarding Dr. Schoeneck's discussion, we must remember that Evans in a very careful study determined that there was a very high degree of hormone content about the sixtieth day of normal pregnancy. This high point must be considered when we make a quantitative estimation of the hormone in the diagnosis of hydatidiform mole or chorioepithelioma. However, it is the increasing amount of hormone which is important.

As to Dr. Novak's comment, he is perfectly right. I did put the percentage of possible cures rather high. My study of the literature revealed the fact that the mortality rate is now only about 10 per cent for women with chorioepithelioma. I merely want to prophesy that with increased interest in the subject, and more definite knowledge regarding the disease, this mortality surely could be cut to 5 per cent. Dr. Novak feels that I have stressed too much the importance of the Aschheim-Zondek reaction and have not paid sufficient attention to the pathologic side in regard to diagnosis. Many of the errors in diagnosis and mismanagement of cases, as seen from a study of the literature, seem, however, to have been due to the inability of the pathologist to arrive at a definite, correct conclusion.

MANAGEMENT OF BREECH DELIVERY IN PRIMIPARAS*

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MOST articles written on the subject of breech delivery present figures concerning fetal and neonatal mortality. This approach is somewhat suggestive of the statement that while people talk a lot about the weather no one really does anything about it. Hence the decision, from a study of fetal and neonatal mortality in one institution over a period of fifty years, to formulate what we believe to be the best method of management of breech delivery in the primipara. It may be added parenthetically that such conclusions as are drawn may be applied with equal force to breech delivery in the multipara, as our experience with both groups has been strikingly parallel.

Table I presents an outline of 2,035 miscellaneous breech deliveries and 58 cesarean sections occurring on the house service of the Boston Lying-in Hospital during the years 1888 to 1937 inclusive. The cases selected from this material are limited to 500 pelvic deliveries and 32 cesarean sections performed upon healthy, primiparous women at full term, whose babies at birth weighed six pounds or more. In accordance with an article previously published[2] we have eliminated from consideration 453 breech deliveries and 6 cesarean sections complicated by factors such as pre-eclampsia, eclampsia, chronic nephritis, syphilis, diabetes, cardiac disease, hydramnios, placenta previa, ablatio placentae, and prolapse of the cord, all of which in themselves add to the gravity of prognosis for the baby. We have eliminated "non-viable" infants, macerated at birth or grossly malformed. We have eliminated premature infants weighing less than 5 pounds at birth, and immature babies weighing from 5 to 6 pounds. Finally, since the subject lies outside the scope of this survey, we have eliminated mature multiparous deliveries.

In computing mortality, stillbirths and neonatal deaths are classified as *mechanical* or *intercurrent*. Deaths from mechanical causes occur from asphyxia or trauma, demonstrable either clinically or by postmortem examination. Deaths from intercurrent causes are due to such factors as congenital heart disease and incidental pathology of early neonatal life.

Table I summarizes the results in the 500 breech deliveries and 32 cesarean sections. The figures, which yield a mortality of 10.2 per cent for all pelvic deliveries and of 3.1 per cent for cesarean sections, do not indicate a rosy prognosis for the infant.

It is at this point that our crude statistics should be analyzed, in order to determine whether in fifty years there has been any trend

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22 to 24, 1938.

toward improvement in our results, and to discuss any possible improvement which may have occurred. The figures of the 500 breech deliveries, recast in another form, will illustrate the point.

During the years previous to 1921 the general management of breech delivery consisted in the classically conservative attitude expressed by the formula, "Leave the case to nature. Guide the trunk until the umbilicus is born. Be ready to assist delivery at any time should delay occur." The first primiparous breech delivery entrusted to me in my intern days in 1920 was conducted in this way. The breech slowly came over the perineum. The fetal heart was suddenly lost. The baby was extracted, stillborn, the placenta, prematurely separated during the second stage, following immediately. On March 1, 1921, Irving and myself undertook a special assignment on breech delivery for one year, conducting such cases both in the Hospital and Out-Patient Department under an activist policy which was expressed briefly as, "Extract at full dilatation." Our results, published in 1926,[4] showed a lowering of primiparous breech mortality from 11 per cent to 7.4 per cent, which we believed justified our policy. This policy has been continued since.

TABLE I. DELIVERIES OF BREECH PRESENTATIONS AT THE BOSTON LYING-IN HOSPITAL FROM 1888 THROUGH 1937

		INFANTS DELIVERED	INFANTS WELL	INFANTS STILLBORN OR DIED	MORTALITY PER CENT
A. Breech deliveries					
1. Uncomplicated	(2,035)				
a. Primiparous	(691)				
(1) Premature		102	45	57	55.8
(2) Immature		89	77	12	13.4
(3) Mature		500	449	51	10.2
b. Multiparous	(768)				
(1) Premature		119	54	65	54.6
(2) Immature		89	85	4	4.5
(3) Mature		560	514	46	8.2
2. Complicated	(453)				
3. "Nonviable" (macerated and malformed)	(123)				
B. Cesarean sections	(58)				
1. Uncomplicated	(52)				
a. Primiparous		32	31	1	3.1
b. Multiparous		20	18	2	10.0
2. Complicated	(6)				

Some further evidence in justification of routine extraction has been adduced from two other sources.

1. A series of 87 consecutive breech cases as a special assignment undertaken by me from Oct. 1, 1931, to Apr. 1, 1933. Eighty-three were delivered through the pelvis with the expectation of securing a live infant, with two neonatal deaths, a mortality of 2.3 per cent.[1]

2. The results of delivery of 351 mature primiparous single infants from 1913 to 1937 inclusive, which show a decrease in intercurrent and mechanical mortality from 9.8 per cent in the years from 1913 to 1920 inclusive, to 5 per cent from early 1928 through 1937 (Table II).

The real difference, however, in the results of the two policies, conservative and activist, did not stand forth in clear contrast until the records of breech deliveries from 1888 through 1912 were tabulated and added to those from 1913 through 1937. This is shown by Fig. 1, and by Table III in which the deliveries from 1888 to March 1, 1921, are

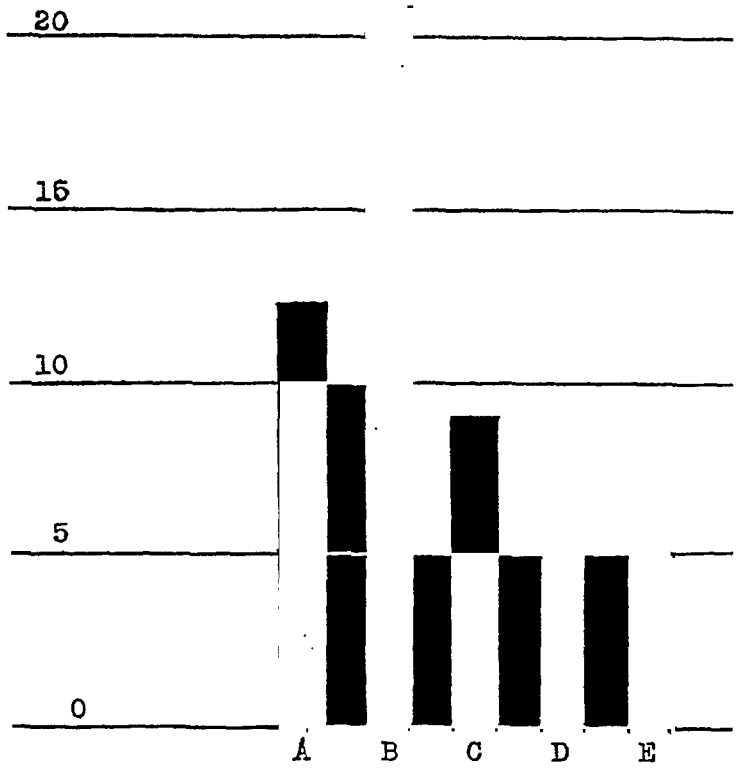


Fig. 1.—Mortality in breech delivery (1888–1937). Primiparous mature single infants. *A*, 1888-1905, 82 deliveries, 10 fatalities, 12.2 per cent; *B*, 1905-1920, 100 deliveries, 21 fatalities, 21.0 per cent; *C*, 1921-1928, 100 deliveries, 9 fatalities, 9.0 per cent; *D*, 1928–1932, 100 deliveries, 5 fatalities, 5.0 per cent; *E*, 1932–1937, 100 deliveries, 5 fatalities, 5.0 per cent.

contrasted with those from the latter date through 1937. The differences between mortality rates of 16.9 per cent and 6.3 per cent for single deliveries and 16.3 per cent and 6.2 per cent for single and multiple are worthy of remark.

It will not be maintained, at this point, that the crude ratio of 16.3 to 6.2 represents, in our experience, the comparative risks to the infant by delivery and extraction. Certain factors in connection with the mechanical deaths in the two periods should be studied first. Table IV summarizes these fatalities, using a classification which has been suggested before.

Group A.—Mechanically easy delivery of apparently normal infants, with neonatal death occurring a few hours to several days later with evidences of intracranial hemorrhage. This group may be likened to those deaths following normal vertex delivery with similar results.

TABLE II. MORTALITY IN BREECH DELIVERY. PRIMIPAROUS MATURE SINGLE INFANTS 1913-1937

	INFANTS DELIVERED	INFANTS WELL	INFANTS STILLBORN OR DIED	FATALITIES		MORTALITY PER CENT.
				INTERCURRENT	MECHANICAL	
1913 -1920	51	46	5	0	5	9.8
1921 -1928(p)	100	91	9	2	7	9.0
1928(p)-1932(p)	100	95	5	1	4	5.0
1932(p)-1937	100	95	5	0	5	5.0

TABLE III. MORTALITY IN BREECH DELIVERY, MATURE INFANTS, BEFORE AND AFTER MARCH 1, 1921

	IN-FANTS DE-LIVERED	IN-FANTS WELL	INFANTS STILL-BORN OR DIED	FATALITIES		MORTAL-ITY PER CENT
				INTER-CUR-RENT	MECHAN-ICAL	
Primiparous, single						
1888—Mar. 1, 1921	183	152	31	1	30	16.9
Mar. 1, 1921—1937	299	280	19	3	16	6.3
	482	432	50	4	46	10.4
Primiparous, single and multiple						
1888—Mar. 1, 1921	196	164	32	1	31	16.3
Mar. 1, 1921—1937	304	285	19	3	16	6.2
	500	449	51	4	47	10.2
Multiparous, single						
1888—Mar. 1, 1921	204	178	26	10	16	12.7
Mar. 1, 1921—1937	300	284	16	4	12	5.3
	504	462	42	14	28	8.3
Multiparous, single and multiple						
1888—Mar. 1, 1921	231	202	29	11	18	12.5
Mar. 1, 1921—1937	329	312	17	4	13	5.1
	560	514	46	15	31	8.2

TABLE IV. MECHANICAL MORTALITY IN BREECH DELIVERY

	GROUP A	GROUP B	GROUP C	TOTAL
1888—Mar. 1, 1921				
Deaths following normal or assisted delivery	1	4	1	6
Deaths following extraction after full dilatation	2	2	7	11
Deaths following extraction before full dilatation	1	0	2	3
Deaths following extraction after manual dilatation	0	0	11	11
	4	6	21	31
Mar. 1, 1921—1937				
Deaths following normal or assisted delivery	0	0	0	0
Deaths following extraction after full dilatation	2	3	4	9
Deaths following extraction before full dilatation	0	1	3	4
Deaths following extraction after manual dilatation	0	1	2	3
	2	5	9	16

Group B.—Mechanically easy delivery, with stillbirth, or birth of a child in manifestly poor condition who cannot be revived or who dies shortly afterwards.

Group C.—Mechanically difficult or traumatic delivery.

The cases in Group A are those in which, prima facie, good results are obtained, the fatal termination being unpredicted at the time of birth. Undoubtedly some factor inherent in the breech mechanism is involved, as shown by Eardley Holland[3] and others, and it is unlikely that any amount of watchfulness or skill in delivery can ever do away completely with this type of result.

The cases in Group B deserve some detailed consideration. It should be stressed again that in this group delivery is easy, but is followed by stillbirth or by birth of a child dying shortly thereafter. The 11 cases are summarized.

1888. No. 4091. Breech on perineum two hours. Fetal heart rose to 170. Baby extracted. Gasped few times. Died.

1889. No. 4422. Normal breech labor. Baby stillborn. All efforts to resuscitate child failed.

1894. No. 6865. Normal breech labor. Fetal heart 172 at entrance at 5 P.M. No further record on this point. Fully dilated at 10 P.M. Baby born at 10:40 P.M. Stillborn.

1897. No. 8586. Assisted breech delivery. Child somewhat asphyxiated. Revived in hot water. Cry feeble. Did not nurse well. Failed. Died third day. "Cause probably difficult labor."

1906. No. 14629. Spontaneous delivery to umbilicus. No trouble with arms or head. Baby gasped. Heart stopped a half hour later.

1910. No. 17201. Extraction after half hour in second stage without progress. One arm extended. Head easily delivered. Baby gasped once or twice. Died in twenty minutes.

1925. No. 32933. Bagged for premature rupture of membranes without onset of labor. Considerable bleeding after bag was expelled. Fetal heart O.K. at first, later began to fall. Easy extraction. Baby stillborn.

1926. No. 35159. Easy extraction at full dilatation. Baby stillborn. No evidence of prolapse of cord or separation of placenta.

1926. No. 36198. Admitted after forty-three hours of labor outside. Fetal heart 180 on admission. Cervix 3 to 4 fingers dilated. Early contraction ring, easily dilated. Extraction without difficulty, with fetal heart O.K. at beginning. Baby stillborn.

1928. No. 39654. Prolapsed foot with os 4 to 5 fingers dilated. No progress in thirty minutes. Traction made on foot. Second leg brought down. Fetal heart lost. Easy delivery from this time on. Baby stillborn.

1931. No. 5506. Easy breech extraction. Forceps to aftercoming head. Baby breathed with head on perineum, but not after delivery. Autopsy showed bilateral tentorial tear, with laceration of vein of Galen.

While trauma may have been of moment in the two Group B cases delivered through undilated cervices, the history of nine of them indicates that the second stage of breech labor is dangerous to the unborn child. In one at least bleeding suggested some degree of placental separation, while in eight others something happened, quite possibly an involvement of the cord. Since it has been shown that frank prolapse of the cord is five times as frequent in association with breech delivery as with the general run of hospital deliveries, this assumption seems worthy of consideration.

The cases in Group C resulted fatally because of frankly traumatic factors. The evidence from the records indicates that pelvic contraction was of moment in only 5 of the 500 deliveries, a surprisingly small proportion, indicating that the judgment of the Staff to allow delivery to proceed via the pelvic route was justified in 99 per cent of the cases. On the other hand, delivery of the infant through an incompletely dilated cervix or following accouchement forcé was strikingly frequent in the Group C fatalities in both periods surveyed, and illustrates the danger to the infant which these maneuvers entail.

The tabulation of these figures has no definite significance in indicating that extraction following full dilatation was more or less dangerous to the infant than normal or assisted delivery. Table V, taken from the records from 1888 to 1912, indicates the mortality in the normal group to be 8.9 per cent, while that in the extracted group was 10.9 per cent. On the other hand 2 of the deaths following extraction occurred in cases in which the pelvis had been misjudged, while, as would be expected, extraction was done during this era only on cases where it was deemed that unassisted delivery would be dangerous or impossible.

TABLE V. COMPARISON OF MORTALITY FOLLOWING BREECH "DELIVERY" AND BREECH "EXTRACTION," 1888-1912

	TOTAL CASES	DEATHS	GROUP A	GROUP B	GROUP C	MORT. %
Normal or "assisted" deliveries	67	6	1	4	1	8.9
Extraction following full dilatation	64	7	2	2	3	10.9

From a priori reasoning there is some ground for the belief that extraction, properly done following full dilatation, might be less dangerous to the infant than the vicissitudes of normal or assisted delivery. The mechanism of breech birth is essentially three-fold in nature, involving successive submechanisms of breech, shoulders, and head. It is stated by Le Lorier,[6] Williams,[8] Piper,[7] and others that the three submechanisms present successively larger circumferences to pass through the birth canal, similar to a truncated cone passing small end first. Von Jaschke[5] states "In footling presentations the danger to the child is increased, in that the circumference of the breech, noninclusive of the legs, is only 24 cm., hence the aftercoming head is the means whereby full dilatation of the os is encompassed." Williams[9] gives the suboccipitofrontal circumference of the head, which later passes through the os, as 34 cm. There are, of course, some differences in these figures according to the size of the infant, but they strongly suggest that full dilatation of the os in relation to the breech is often insufficient dilatation for the aftercoming head. Should full dilatation for the breech mean insufficient

dilatation for the shoulders, extended arms are sure to result. Very little experience with breech delivery, indeed, is required to appreciate the fact that extended arms are common, and that delivery of the head is often associated with a sense of resistance as the head passes the cervix.

Before concluding this phase of the subject one other factor should be considered. Prior to 1921 little if any medication was used during labor. The patient's second stage was conducted with her cooperation, good or bad though it might be. At the most, ether to the obstetric degree was given. When and if progress was delayed, it became necessary to anesthetize the patient. This was often a hurried performance and by the same token the manipulations carried out were often hurried and therefore relatively poorly done. Subsequent to 1921 the policy of breech extraction was carried out under full surgical anesthesia from the start. More time could be taken to do a slow and methodical extraction without any sense of frantic haste. More recently analgesic medication has been the order of the day. Conscious effective cooperation of the patient in the second stage, if it were desired, has been practically abolished, while at the same time the human impulse to "do something" before full dilatation has undoubtedly been kept in abeyance.

It is for the foregoing reasons that we believe that our policy since 1921 of extraction during the second stage of labor has paid dividends in a reduction of our stillbirths and neonatal fatalities. While we are not dogmatic in the original concept of extraction *immediately* at full dilatation, we believe, nevertheless, that extraction under complete anesthesia after full dilatation has been attained is safer for the infant than normal or assisted breech delivery.

Thus far the subject of cesarean section for primiparous breech delivery has been barely touched upon. If we recall the history of this operation in general, we are reminded of the fact that it is primarily undertaken in the interest of a living child which cannot pass through the pelvis of its maternal host. The diagnosis of cephalopelvic disproportion is relatively easily made in the case of the vertex presentation, and may, under proper supervision, be delayed until a test of labor has given the final answer. On the other hand, when the breech presents, the fetal head is the last and largest end of the cone destined to pass through the pelvic girdle, and the test of labor, so useful in vertex presentation, is quite out of the question.

Despite this unfavorable aspect of the situation there are still some favorable factors. The size of the baby's head can often be more accurately estimated when it lies in the fundus than in the lower abdomen: in fact the size of the entire baby can often be more clearly made out by clinical palpation; in our series all four cesarean sections done "for large baby" yielded infants weighing over 9 pounds. Finally, clinical measurements of the pelvis, both external and internal, are equally available regardless of the nature of the presentation.

We have had some hope that measurement of the head in the fundus by stereo-x-rays might help in elucidating this problem of cephalopelvic adaptability. It has unquestionably been of value in the diagnosis of hydrocephalic and anencephalic infants, the delivery of which alive, setting aside religious scruples, is to be deprecated. It is successful in giving an accurate measurement of the silhouette of the baby's cranium in 65 per cent of the cases at the first attempt. On the other hand this silhouette is that of the occipitofrontal plane in 89 per cent of the cases, of an oblique plane in 3 per cent, and of the important biparietal plane in only 8 per cent;[1] consequently *the* essential biparietal diameter must be estimated within limits from the occipitofrontal diameter before it can be compared with the patient's conjugata vera. Finally, while the stereoroentgenometric technique which we have used has not yet satisfied us that it measures the maternal pelvis accurately, we can still avail ourselves of digital measurement of the pelvis, under anesthesia if necessary.

The results of our 32 uncomplicated primiparous breech cesarean sections have been shown in Table I. The one neonatal death in the series occurred on the eleventh day post partum from intercurrent erysipelas, so that no fetal mortality from mechanical causation has occurred. All the mothers survived. The neonatal deaths occurring after two multiparous breech cesarean sections resulted, respectively, from impetigo and hydrocephalus (the latter in 1918).

Table VI reviews the 32 sections according to indication, dividing them into two groups, those before 1932 and those in 1932 and subsequently when x-ray investigation was started.

It is noticeable that in both groups the majority were for contracted pelvis, elderly primiparity, or estimated large babies. That the estimate of the weights of the large babies was accurate has already been com-

TABLE VI. INDICATIONS FOR CESAREAN SECTION IN PRIMIPAROUS BREECH DELIVERY

	NO. CASES	X-RAYS
1911 through 1931:		
Contracted pelvis	7	0
Active tuberculosis	1	0
Elderly primiparity (37, 38, 44)	3	0
Ankylosis of left hip	1	0
Estimated large baby (9 pounds 8 ounces)	1	0
	13	0
1932 through 1937:		
Cephalopelvic disproportion by clinical and x-ray measurements	7	7
Elderly primiparity (41, 42, 43)	3	1
Estimated large babies (9 pounds 5 ounces, 9 pounds 5½ ounces, 9 pounds 11 ounces)	3	3
Funnel pelvis	2	1
Flat pelvis	2	0
Longstanding rupture of membranes without labor	2	0
	19	12

mented on. Elderly primiparity certainly deserves consideration in deciding upon cesarean section for primiparous breech delivery, for an expected fetal mortality of 4 to 6 per cent may be a high price to pay for delivery through the pelvis of what is likely to be the patient's only child.

CONCLUSIONS

1. The cases discussed in this survey have been limited to normal primiparas at full term with living undeformed infants in utero all weighing 6 pounds or over. Study of the records and treatment of the 532 deliveries has been undertaken to determine the proper management for such cases in the future.

2. The management of breech delivery resolves itself primarily into an estimate of the relative advisability of abdominal section versus delivery through the pelvis.

3. Minor degrees of pelvic contraction are very important when the breech presents, since the test of labor as applied to vertex presentations is of no value for the aftercoming head.

4. The size of the infant in utero must be carefully considered. X-ray measurements have proved to be of value in helping to arrive at this estimate.

5. It is a wise policy to use the x-ray in any case in which abdominal delivery is contemplated, not only to confirm and control the size of the infant but also to detect gross skeletal abnormalities undiscovered by clinical examination.

6. The age and fertility of the mother must be considered.

7. If pelvic delivery is selected the second stage should be terminated by breech extraction under full anesthesia before the birth of the umbilicus, as classically recommended, has occurred.

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475 Commonwealth Avenue

DISCUSSION

DR. ARTHUR H. BILL, Cleveland, Ohio.—In Dr. Goethals' splendid paper he has backed up by convincing statistics his claim that extraction at the time of full dilatation is preferable to assisted birth. I am in absolute agreement with this and see no reason whatsoever for allowing labor to go on in a breech case after full dilatation. This has been my policy throughout my entire practice, and I could add statistics to prove this point.

Of course, we must first of all rule out those cases in which there is a disproportion between the bony pelvis and the fetal head. Since there is no such thing as a test of labor, this should be done before labor by careful measurements and x-ray. Inasmuch as there is some error in measurements of the fetal head and pelvis, I think that where there is a reasonable doubt as to the probability of the

head passing through the pelvis a cesarean section should be done. When the baby is to be delivered through the pelvis the secret of success is in having the way clear for its passage through the entire birth canal, that is, by removing as far as possible the resistance of all the soft parts, including especially the cervix and lower uterine segment. Resistance of the cervix and lower uterine segment is probably responsible for most of the bad results in cases of breech presentation.

When delivery is performed at the time of full dilatation the patient is put under a complete anesthetic and the vaginal canal is ironed out thoroughly by manual dilatation. Usually an episiotomy is performed. The hand is then passed up through the os and full dilatation is assured. Estimation of the size of the os is made by spreading the fingers as far as possible to what would be the size of the aftercoming head and not merely the size of the breech. Then the lower uterine segment is relaxed by complete anesthesia. Relaxation by anesthesia is very important. If these precautions are taken, the arms very seldom go up over the head during extraction. In assisted birth when the breech descends to the perineum and uterine contractions are continuing, the precautions mentioned are not taken. The vaginal canal has not been ironed out and is more or less resistant. The cervix may not be dilated to the size of the aftercoming head and the lower uterine segment is not relaxed. If the arms go up over the head it is usually because they are drawn up by the resistance of the cervix and lower uterine segment. The same resistance makes delivery of the aftercoming head difficult. These few points illustrate the advantage of performing the extraction early rather than waiting and allowing the patient to do as much as she can. We must also bear in mind that the easiest time to bring down the legs is when the breech is high rather than when it is low down in the pelvis.

I would like to sum up what I think are the important steps in the management of a breech delivery. When there is full dilatation proceed to deliver the baby. Thoroughly iron out the whole vaginal canal and usually perform an episiotomy. Never take for granted that the os is dilated even though the breech has passed through it. Examine the cervix and dilate the os manually if necessary. Relax the lower uterine segment by complete anesthesia, bring down both feet, one at a time, and do the extraction. Do not use the Mauriceau grasp but deliver the aftercoming head by suprapubic pressure on the head aided by the guiding traction and flexion produced by the finger in the child's mouth. Be sure that the head does not lie in the anteroposterior diameter of the pelvic inlet. Rotate the head so that it will enter the pelvic brim in the transverse or oblique position. Forceps on the aftercoming head are, to my mind, rarely necessary. If this procedure is followed I see no reason why there should be much more difficulty in extracting a breech in the case of a primipara than in that of a multipara, or following a podalic version.

DR. WARD F. SEELEY, DETROIT, MICH.—I have reviewed the cases of breech delivery from two of our Detroit hospitals for a five-year period. One of these is a charity, teaching institution, the other a private hospital. In both the essential principle of management was essentially the same for breech delivery, that is, interference only when indicated. The fetal mortality by this more conservative treatment in our hands is practically the same as that reported by Dr. Goethals.

For a period of five years there was a total of 13,685 deliveries among which were 773 breech positions. Of these, 270 were in primiparous women. If deductions are made for cases of toxemia, placenta previa, prolapse of the cord, abruptio placentae, nonviable infants, etc., as suggested by Dr. Goethals, in order to arrive at a true rate of risk from breech position itself, we have 182 cases upon which to base our opinion. To arrive at this figure we have deducted twins and nonviable prematures, but have included all cases of eight months' duration or more and all infants weighing 5 pounds or more. In other words we have made no deduction for Dr. Goethals' classification "immature." We made this slight departure from Dr. Goethals' classification because our cases include a number of colored women, whose babies, although well developed, usually average less in weight than the white, and also because we feel that a fetus of eight months should have an excellent chance of surviving.

Among the 182 uncomplicated, mature, single primiparous breech deliveries, there were 9 fetal deaths or 4.9 per cent. There was no maternal mortality.

Six babies were stillborn and 3 died in the neonatal period. Five deaths occurred in cases with breech extraction and four after spontaneous delivery. All but one death were probably the results of birth trauma.

There were only 2 cesarean sections for pelvic contraction in the 270 cases. I can agree with Dr. Goethals that the proper evaluation of methods of delivery in these cases is difficult. And all information obtainable, both clinically and by x-ray examination, is none too much.

In conclusion, let me state that we are not opposed to breech extraction as evidenced by the fact that 42.2 per cent of our series were thus delivered, but we prefer to use it only upon indication. We also believe that the indication will arise less often if deep analgesia in the second stage is avoided.

DR. J. M. BERGLAND, BALTIMORE, MD.—We have had some recent reports from the obstetrical clinic of the University of Maryland which indicate that the operation of external version is not as difficult as we had supposed. My own experience with this procedure has been very discouraging, but I believe that, in view of this report which has not been published, we will give the matter at the Johns Hopkins more attention.

Many years ago I helped Dr. Williams do the first pubiotomy ever performed in the city of Baltimore. The operation has now been almost entirely discarded in view of new procedures such as low cervical cesarean sections, which are now very properly in vogue. However, I still think there is a place for pubiotomy. In many cases we are uncertain as to the size of the aftercoming head in spite of the most modern methods for measuring this part of the baby and quite often we underestimate the diameters of the head and have to end up with a craniotomy in order to deliver the child. I believe that when we are in grave doubt as to the question of disproportion we should place the Gigli saw in position and then if attempts to deliver the head fail, we can complete the operation of pubiotomy by cutting through the bone and the child's head can then be freed without special difficulty. If the full operation is not necessary the saw is removed and no damage is done.

DR. GEORGE W. KOSMAK, NEW YORK CITY.—Dr. Goethals did not go into the details of the technique which he employed in these cases. I would like to know whether at any time he made use of the Voorhees' bag? There is a group of breech presentations in which the bag can be used with advantage to secure that satisfactory dilatation of the cervix which is so essential. I admit that these cases must be rather carefully selected and probably in the greater number of breech cases it is unnecessary, and yet an experience with two women within two weeks convinced me of the desirability of that procedure. One was a primipara in the eighth month who had a very rigid cervix, the other a multipara with a thick cervix, at term. In both of those cases I used the Voorhees' bag, using next to the largest one in the primipara and the largest size in the multipara. I think the rupture of the membranes might have swept the cord down but the insertion of the bag improved the chances of getting a satisfactorily dilated cervix.

I hoped that Dr. Bill would mention the protection of the child with a warm towel as it is born. I think the respiratory efforts on the part of the baby are very often stimulated by the cold air of the immediate surroundings. You must remember that the temperature inside is about 98 and outside is very likely to be 65 or 70. The envelopment of that baby in a warm towel as it is being born is very important.

DR. WILLIAM T. McCONNELL, LOUISVILLE, KY.—In breech presentation it is especially difficult to determine the relationship of the fetal head to the pelvis. While it is true that ordinarily the head will correspond in size to the size of the baby's body, and while it is true that the way the pelvis of the baby comes down into the pelvis of the mother will give you some idea as to the relative ease with which that head will pass through, yet it is often a very difficult thing to tell what the relationships are. A number of things may help us. One is the history of the size of the babies this mother has already had; another is the acumen with which we are able to palpate the size of the baby in this mother; another is the use of the x-ray, to determine to a minute degree the size of the pelvic inlet.

DR. IRVING W. POTTER, BUFFALO, N. Y.—I was very much pleased to hear Dr. Goethals use an expression which no one else has used here today, that is the "misjudged" pelvis. Now if it is true, as I believe, that breeches occur more frequently in the funnel-shaped pelvis, we are then usually dealing with more or less of a contraction. In women who are past 35 or 40, who have never had a child and will probably never have another, we lean to the operative side, that is, cesarean section.

Our technique is a little different than what has been described. As soon as the lower uterine segment is effaced and the os is dilated we bring down both feet and terminate these cases as footlings. We deliver the baby slowly and carefully by traction as far as possible. If the child does not move we do not pull it until we find where the obstruction is. Then as the scapula appears we put a finger in the posterior axillary fold and deliver both shoulders as anterior shoulders, never going up and pressing as we used to do and having a paralyzed arm. The operation of episiotomy we never do. It seems to me an operation entirely unnecessary. But we do use the Piper forceps more often as years go on.

Dr. Kosmak spoke of protecting the baby to prevent it from breathing too soon. We have watched babies in our versions make respiratory efforts and have seen no harm ever come from it. We never wrap a baby unless it is so slippery that we cannot hold it.

DR. GOETHALS (closing).—We agree with Dr. Bill's practice in regard to using forceps on the aftercoming head according to indications. We try pressure on the head from above first. If this does not work, the use of forceps is a life-saving measure without doubt.

Comparing our statistics as best we could with those of others we found that by taking the same types of cases we had about the same results. I am not entirely certain that in the long run, with many thousands of cases, the policy of routine extraction after full dilatation will necessarily be any better than the other policy *in the same man's hands.* Of course, if external version can be done it is by all odds the thing to do. If we have a 6.2 per cent mortality in primiparous breech delivery and less than 1 per cent in normal vertex delivery, the advantage of having the baby turned is perfectly obvious.

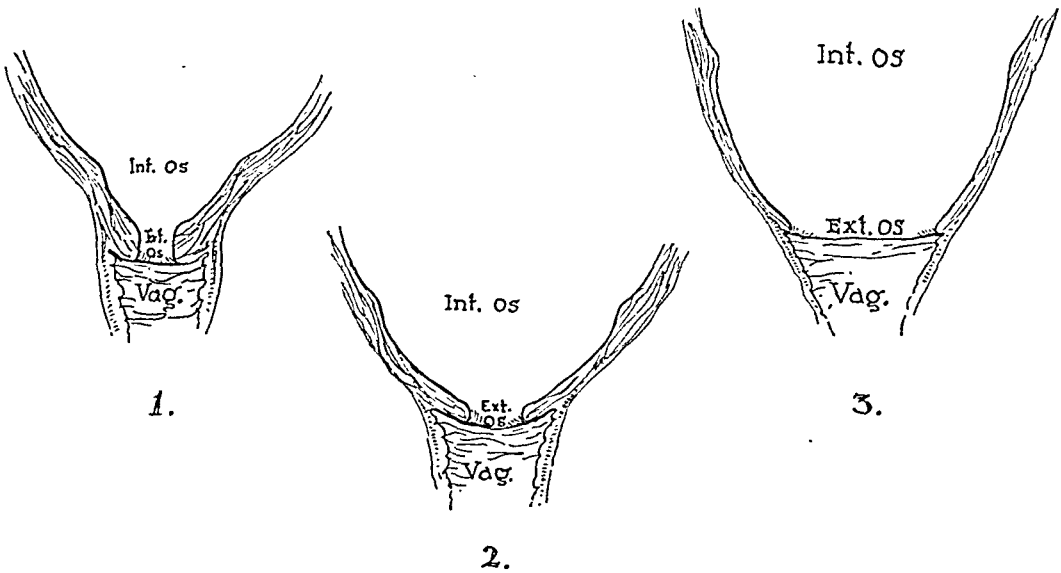
In two or three instances we did use the Voorhees' bag. The indications were particularly for premature rupture of the membranes and lack of progress of the first stage. We do not use hot cloths to wrap the baby in, because we feel that a few respiratory efforts do no harm if the accoucheur is sure he can get the baby out without asphyxia resulting.

THE PITFALLS OF PODALIC VERSION AND EXTRACTION*

MILTON G. POTTER, B.A., M.D., F.A.C.S., BUFFALO, N. Y.
(From the Millard Fillmore Hospital)

IN THE performance of internal version, I believe that it would be advantageous to recall again not only that deep anesthesia, "ironing out" of the vagina, the modified Walcher position and lack of haste are essential prerequisites, but also to emphasize some of the things the operator should not do, when attempting this type of delivery, which have not been written about before.

The purpose of this paper is not to deal with the indications for this procedure but rather to impart the results of our experiences, and always to keep in mind the following precautions.



Figs. 1 to 3.—Degrees of effacement of the lower uterine segment and dilatation of the external os.

1. *Never Attempt a Version and Extraction (Nor Any Other Type of Delivery) Until the Lower Uterine Segment Is Effaced and the External Os Completely Dilated.*—The careless or ignorant observance of this rule has done more to discourage the use of this operation than all other factors and this peculiar situation arises, I believe, from the lack of a uniform and fixed definition of complete dilatation of the os.

It has been the custom in our teaching in recent years to avoid the term dilatation of the cervix entirely, and speak only in terms of the degree of effacement of the lower uterine segment and the degree of dilatation of the external os (Figs. 1, 2, 3). Our distinct impression is that too little attention is paid to the lower uterine segment in labor and that it is the rule rather than the exception to find obstetricians failing to recognize the distinction between incomplete effacement of

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

the lower uterine segment with a rigid, nonnegotiable cervix and complete lower uterine effacement with a paralyzed external os, which appears not to be completely dilated, but which disappears under deep anesthesia, when the examining fingers are spread apart and allows the entrance of the hand into the uterus.

It must be remembered that the crux of the situation is the complete effacement of the lower uterine segment and that dilatation of the external os is one of degree only.

Effacement begins before the onset of labor and when it is complete we have the beginnings of a retraction ring which is relaxed under deep anesthesia so that version can be completed.

We consider the external os dilated when the lower uterine segment is completely effaced and the external os, under deep anesthesia, admits three fingers and when spread readily admits the hand into the uterus. This is not saying we deliver the patient when the cervix is three fingers dilated, for it must be remembered that there may be a three finger dilatation of the external os without complete effacement. In other words in the first instance, we have a paralyzed external os with a possible rim present which melts away under easy pressure of the fingers, along with complete effacement of the lower uterine segment, and in the second instance, we have a three-finger dilatation without complete lower uterine effacement which means we have a nonnegotiable external os which will not admit the hand without tearing and is therefore not dilated.

Not infrequently we see arrest of the fetal head in midpelvis.

The lower uterine segment is effaced, but the head which is in the transverse or posterior position is above the external os, which is perhaps three fingers dilated and will never become more dilated because of the absence of the head as a dilator at the external os. It is a flaccid, paralyzed external os which will become swollen and edematous if delivery is not effected at once.

2. *A Version Is Best Attempted When the Head Is at the Brim and Has Had a Chance to Mold.*—The prevalent opinion that an ideal case for the use of version and extraction is a floating head is erroneous. The head should, at least, be at the brim and there should be partial molding of that fetal head with flexion, if the operator expects his extraction to be successful. If the pelvis is large and the baby small, it is possible that no difficulty will arise, because the head can be pushed into the pelvis from above, but given a slightly contracted pelvis and a normal-sized baby, with no molding of the head, the operator will expose that fetal head to injury, just as he would in the delivery of the aftercoming head of a breech case with similar pelvic and fetal measurements.

It must be remembered that a floating head, even though it can be pushed into the pelvis, is the type of case which carries a greater risk, and we can therefore expect a higher fetal mortality rate.

3. *A Version Should Never Be Attempted When the Uterus Is Dry and Firmly Contracted Around the Fetus* (Fig. 4).—Failure to heed this warning may easily result in rupturing the uterus and yet we have

seen attempts to do version under these conditions. Of course this does not exist excepting after a long labor, ruptured membranes and molding of the uterus about the fetus and, in the presence of a retraction ring, unsuccessful attempts with forceps. Then the operator, with his obstetric judgment affected perhaps by fatigue, tries a podalic version, and the result is a dead baby and often a ruptured uterus.

4. *When the Gloved Hand and Arm Are Once Introduced Into the Uterine Cavity, They Are Not Withdrawn Until Both Feet of the Baby Are Delivered.*—The practice of introducing one hand and then the other in an attempt to grasp the feet of the baby is to be discouraged be-

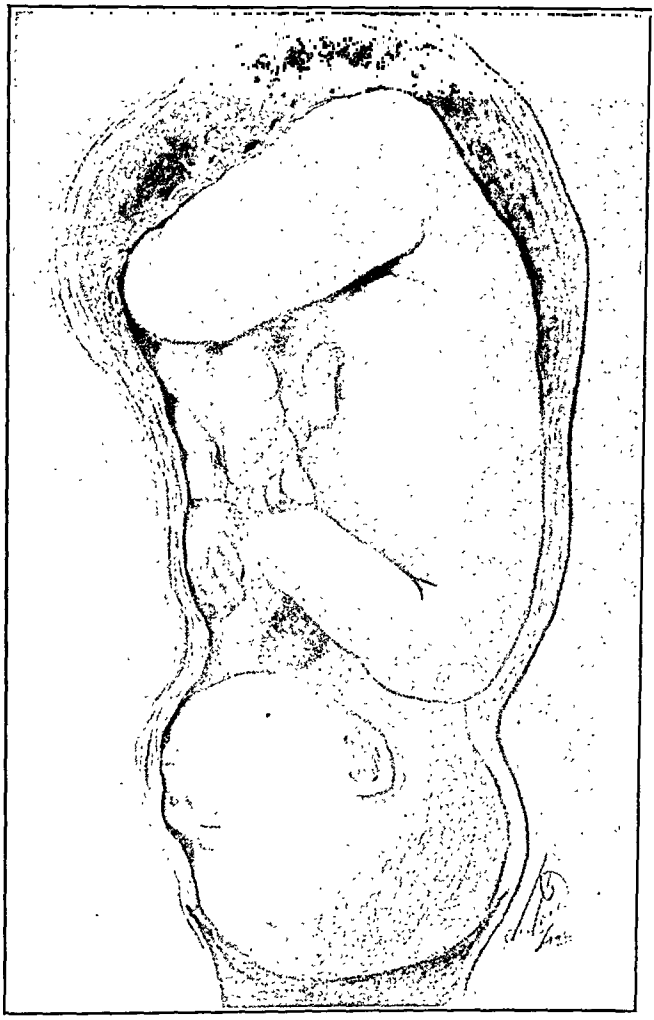


Fig. 4.—Impossible case for version and extraction.

cause of the possibility of infection. If difficulty is encountered in locating the second foot, slight rotation of the body of the fetus will aid the operator in discovering the lost foot.

5. *Never Proceed With an Internal Podalic Version and Extraction Unless the Operator Is Positive that the Arms of the Fetus Are Folded Across the Chest.*—We believe and teach, if the baby's arms have extended, the operator alone is to blame, because he either failed to fold

the arms or he did it carelessly. If there is an excess of amniotic fluid and the arms tend to float away from the folded position, it is a simple matter to allow some of the fluid to escape.

It is rarely possible for the arms to extend if they are folded across the chest, because the chin of the baby keeps them from being dislodged upward and the pressure of the uterine musculature aids in keeping them in place. The rather general idea that the arms are normally in that position is false (Fig. 5), and in many cases we find an arm either alongside the body or the head and any attempt to extract that baby with an arm or arms in those positions will invariably produce an extended arm or arms.

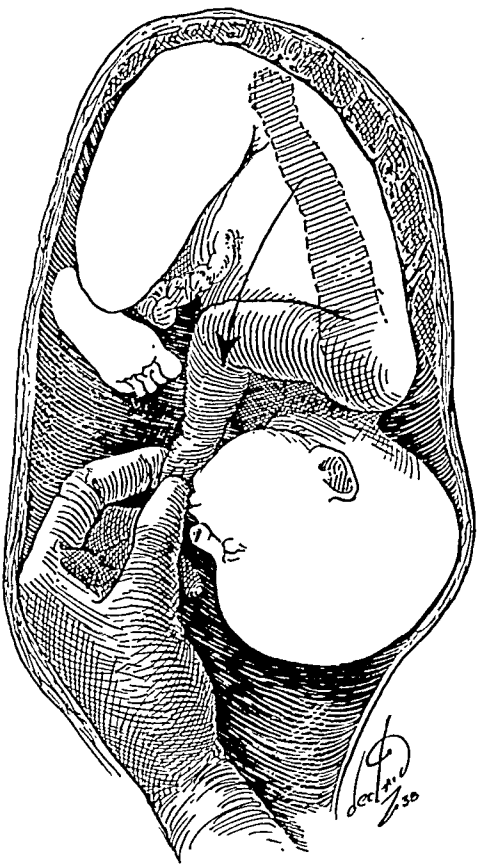


Fig. 5.—Folding arms across chest.

We feel this is so important that we now re-check the position of the arms before the legs are delivered, in order to be positive that the arms are in the proper position, before the version is attempted.

6. *Too Much Traction Should Not Be Exerted in the Delivery of the Feet.*—This warning is given because operators employ too much force in pulling on the feet and when the feet are delivered as far as the vagina, it is found impossible to complete the extraction.

The probable explanation is that the operator failed to feel the fetal head through the abdominal wall, and although he went through the motions of pushing the head up out of the iliac fossa with his external

hand, the head remained lodged in the iliac fossa and the position of the fetus might now be compared to a half-opened jackknife, the point of the blade representing the head and the tip of the handle the feet. Continued traction will certainly rupture the uterus unless the operator remembers to release his grasp of the feet entirely and explore thoroughly the interior of the uterus. He will invariably find the fetal head still lodged in the iliac fossa and if he will place the head in the hollow of his hand and push it up into the fundus, holding it there by his external hand, while he again grasps both feet, he will find that the legs can be delivered with ease (Figs. 6 and 7).



Fig. 6.—Jackknife position of head and feet.

7. *Avoidance of Arm Injuries Can be Accomplished by Doing Away with Pressure on the Upper Arm.*—It is pretty well agreed by all familiar with this subject that delivery of both shoulders in succession, as anterior shoulders, is a decided improvement in the extraction. This maneuver is accomplished by placing the finger at the angle of the scapula, after the scapula appears at the vulva and *not* in the axilla. At this point of the delivery, the scapula is pushed anteriorly under the pubic arch.

A serious fault which many obstetricians have is that after successfully delivering the shoulders, they invariably fail in the delivery of the arms and subject the baby to a possible paralysis of the humoral

nerve, by deliberately placing the index or middle finger on the deltoid region, and try to extract the arm by sweeping the finger downward and hooking it with considerable force around the humerus (Fig. 8).

Much easier and safer is the method of entirely avoiding the deltoid and humoral regions and delivering the arm by placing the finger directly in the bend of the elbow and then lifting the arm up over the chest like a pump handle, thereby avoiding nerve injuries and a possible fracture of the humerus.

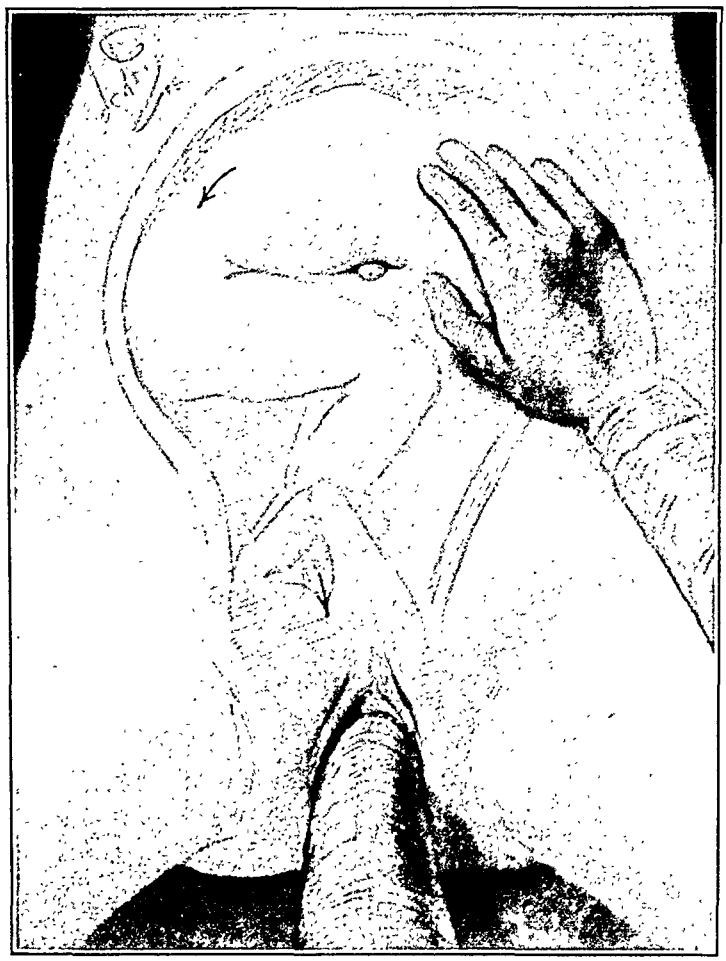


Fig. 7.—Holding head in fundus with external hand.

8. *Avoid Excessive Traction in Delivery of the Aftercoming Head.*—It is not uncommon to see terrific traction exerted upon the neck of the baby in a hurried effort to deliver the head. The back of the baby, therefore, is bent too far upward toward the mother's abdomen. It is essential that flexion of the head and body be maintained at all times. The possibilities of fracture of the clavicles and injuries to the neck and head are great, if the operator forgets that it is much easier and much safer to push a head through the pelvis than pull it through. Omitting this precaution has led to the fracture of the neck of the baby and its death. Maintaining flexion of the head by pressure on the chin, moderate pressure from above and moderate traction from below provides a successful delivery.

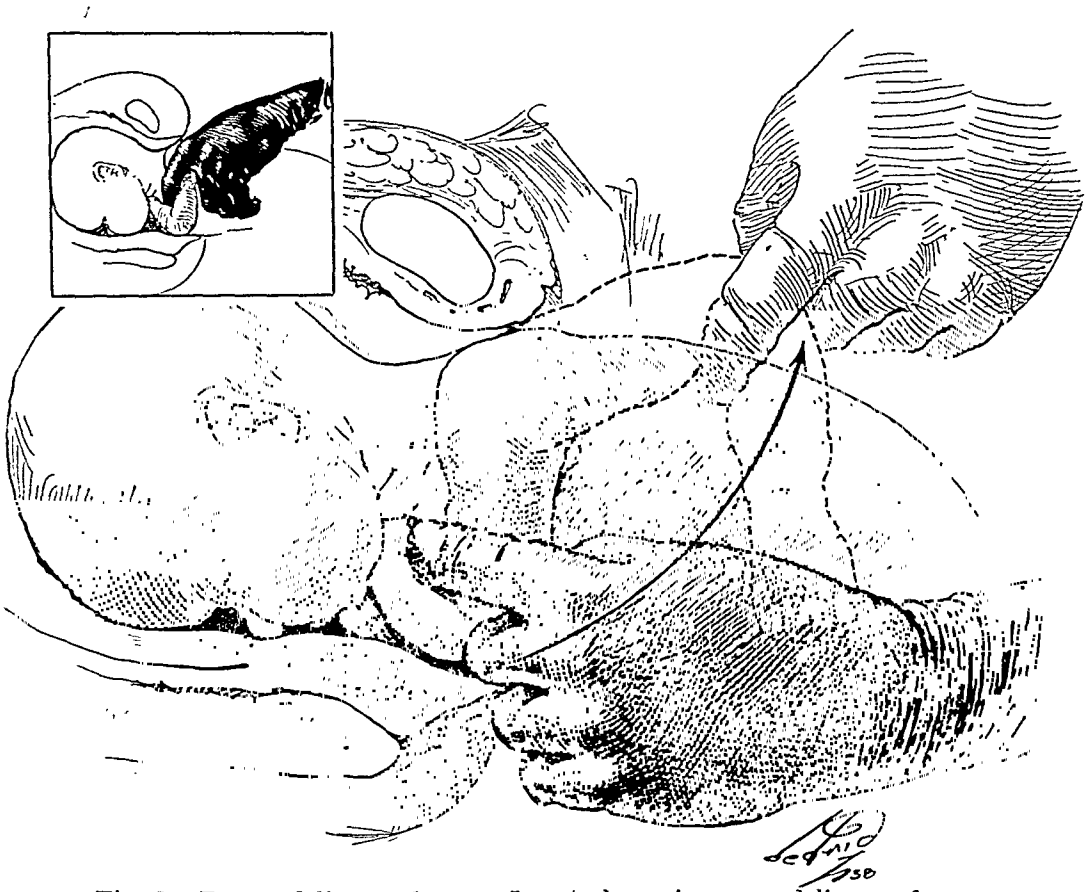


Fig. 8.—Proper delivery of arm. Insert shows improper delivery of arm.

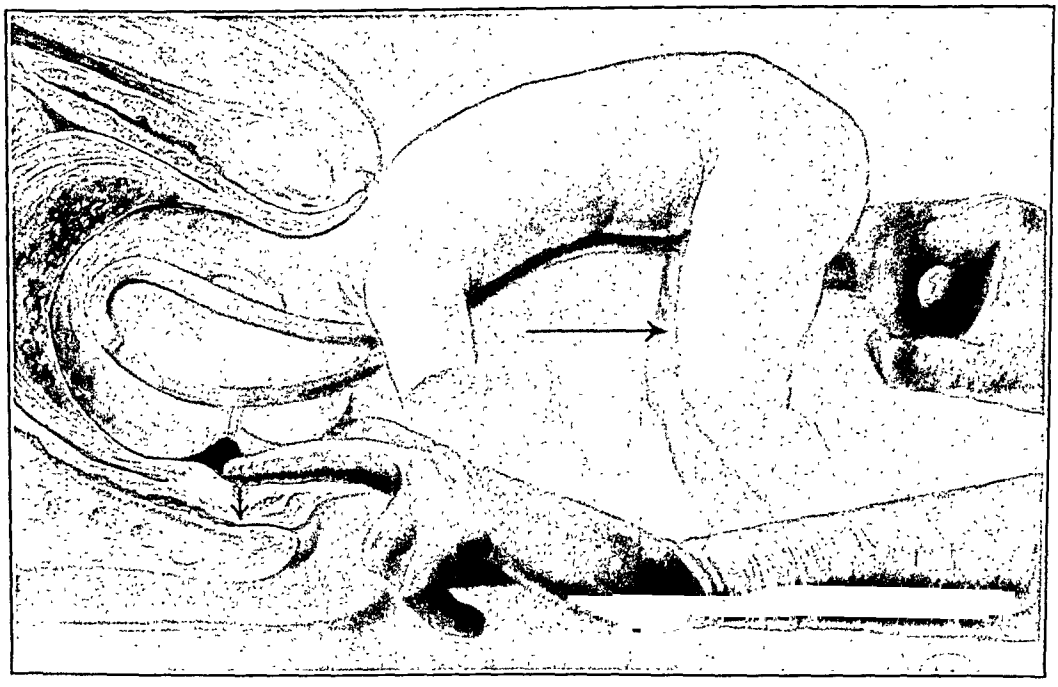


Fig. 9.—Pressure being exerted on perineal body when Piper forceps are used.

If, as sometimes happens, there is an unavoidable extension of the head which cannot be corrected by pressure of the operator's fingers on the chin, or pressure on the head from above, then the use of the Piper forceps is indicated.

9. *Never Attempt the Use of the Piper Forceps on the Aftercoming Head Which Is Not Well in the Pelvis.*—Too often the use of the Piper forceps is resorted to, when the head is either not in the pelvis at all, or is high in the pelvis. It is far better to push the head down into the pelvis as far as possible and then, if difficulty is encountered, to apply the Piper forceps to the sides of the head. The difficulty usually encountered is either a large or an extended head, which can be corrected by the proper use of the forceps. By that I mean flexion of the head can be increased by lowering the handles before locking the forceps (Fig. 9).

As the head descends, obstruction and resistance usually are encountered in the perineal body. The latter, if pressed down by the index or middle finger of the left hand, partially introduced into the vagina, will be depressed sufficiently to allow the chin to slide over it, thereby avoiding a lacerated perineum or the necessity of an episiotomy.

Occasionally in a flat type of pelvis, it is much easier to push the head into the pelvis if the head is grasped and rotated transversely by the external hand, thus making use of the largest diameter of that particular inlet.

And finally we are, at the present time, very prone to use Piper forceps on the small, premature aftercoming head, for we feel that trauma to such a head is minimized by the use of forceps.

186 CHAPIN PARKWAY

DISCUSSION

DR. BERTRAM H. BUXTON, PROVIDENCE, R. I. (by invitation).—In the last ten years at the Providence Lying-in Hospital in some 26,000 deliveries, there have been only 307 versions and extractions, about 1 in 80 deliveries. None of these is of the elective type, except for the delivery of the second of twins. The number has gradually decreased each year from 75 in the first year and a half, to 10 in the year 1937. This has resulted from the increase in the incidence of cesarean section, because we have recognized earlier in labor the case in which formerly version and extraction were resorted to after failure of high forceps.

The statement is made that "A version should never be attempted until the greatest circumference of the head is at least within the pelvic brim and has had a chance to mold." Given the premise that we are going to do elective versions, this is perhaps good advice, but to my unconverted mind a head already molded to come through as a vertex would be much easier delivered by forceps as a vertex.

In regard to the statement that, "if after a reasonable length of time the operator is unable to get both feet, he should then stop and proceed with another method of delivery," I should like to ask Dr. Potter what method he would then recommend. I would rather take a chance on delivery with one foot than to attempt a high forceps on a floating head or a cesarean section after so much manipulation.

DR. A. K. PAINE, BOSTON, MASS.—Some versions fail, not because the nondilatation of the cervix is unrecognized, but because the operator assumes that dilatation will complete itself easily during the delivery. These are errors in judgment rather than inability to recognize the nondilated cervix.

The precaution "never proceed with a version and extraction until the operator is positive the arms are folded across the chest," is of interest. It is further stated

that "Normally in 50 per cent of the cases, the arms are in some other position than across the chest, and extraction in such a case *invariably* produces an extended arm or arms."

In a normal breech delivery an extended arm is not very common unless the operator indulges in questionable procedures to hasten delivery. In versions and extractions as they are generally done surely an extended arm is not encountered in half the cases. By the Potter reasoning noncompliance with this precaution should result in prolapsed arms in approximately half the cases. That certainly is not the general experience.

As regards the importance of not applying force directly to the shoulder or humerus in delivering an arm, it has been my experience that if that downward traction on the body, which delivers the anterior shoulder, is continued long enough the arm will be spontaneously delivered in a large proportion of the cases. The same applies to the posterior arm after its rotation to the front. Digital delivery of the arm is reserved for those cases in which the above technique is not easily successful.

DR. T. L. MONTGOMERY, PHILADELPHIA, PA.—Considering the wide field in which the Potters apply version and the early stage of labor in which they institute it, it is doubtful that all the details of procedure which they recommend are applicable to the indications and conditions under which most of us select the operation, namely, in transverse position, prolapse of the cord, and some of the head presentations in which deflection or malposition calls for a corrective obstetric procedure.

If one is to perform elective internal podalic version and extraction upon all obstetric patients, then one can conceive of the advisability of manually dilating all cervices, starting the version before the membranes rupture, and seizing both feet of the fetus to perform the turning. Under normal indications, however, one is faced with conditions under which the membranes have ruptured, considerable amniotic fluid has drained away, and the uterus so firm that it is not always possible, feasible, or wise to attempt to reach both lower extremities. Under such circumstances it is often easier to deliver the posterior arm in the hollow of the pelvis than to attempt extraction of the anterior. I am of the opinion, therefore, that the old style of version is oftentimes better adapted to the peculiar circumstances of normal obstetric practice than are some of these manipulations recommended by Dr. Potter.

My own observations of the Potter version as performed by Dr. Potter himself are that the cervix is not always completely dilated or nearly so when version is undertaken, and that, therefore, the major portion of the dilatation must be accomplished by manual manipulation; second, that inasmuch as the version is done early in labor and before the membranes have ruptured, there is actually and practically no time for molding of the fetal head before the version is accomplished; third, that cesarean section is performed in many instances in which a better test of labor might have eventuated in normal head-first delivery; and fourth, that as an end result rupture of the uterus in subsequent pregnancies, with sacrifice of the fetus, is not uncommon.

While the Potters have perfected themselves in this form of version and evidently have few accidents, those who have endeavored to emulate their efforts in other cities have often met with disaster. In the records of our maternal welfare work in Philadelphia, there is no more depressing period than that during which a certain school of obstetricians undertook the Potter method of version in a high percentage of their deliveries. The same has evidently occurred in other cities.

This being the case, it would seem to me far more important to collect and report before this organization the maternal and fetal mortality that has resulted from the attempts to follow this form of obstetric practice than to lay further emphasis upon its technique. With such knowledge at hand we should be able properly to evaluate this procedure and doubtless relegate it to the position for which it is intended in obstetric practice—a serious operation to be performed only in the face of definite obstetric indications.

DR. GEORGE M. SHIPTON, PITTSFIELD, MASS.—This paper lays stress on the points to be brought out in case one has to do a version and extraction. While we

may not approve of this method of delivery as a routine method of procedure, the Potters have taught us more about the procedure than any one in the literature.

DR. ARTHUR H. BILL, CLEVELAND, OHIO.—Delivery through an undilated os is responsible for more trouble than any other mistake. This is true not only in versions but in any attempt to deliver a baby. I am opposed to manual dilatation except in an emergency. After my discussion of the breech cases yesterday, I was told that I might have given the impression that I advocated manual dilatation of the cervix. I wish to correct any such impression, for I am absolutely opposed to that in principle and simply said that what we call full dilatation in the case of a breech is not enough dilatation for the aftercoming head, and that when the breech has dilated as much as it possibly can, it may be necessary to iron out the cervix enough to remove any possible resistance to the shoulders and head.

Dr. Potter stressed folding the arms across the chest. Frankly I have never taken this seriously. I believe that the reason why the arms do not go up in his cases is not so much because he folds the arms over the chest as because he has the advantage of wonderful anesthesia with complete relaxation.

There are a certain number of cases in which the head will not enter the pelvic brim while in the abnormal position and yet will pass through very readily if in a normal position. In such cases, I think, I go a little bit further than Dr. Potter and perhaps do versions in some cases in which he performs cesarean sections. Therefore I would not say that the head must be through the pelvic brim and molded as a necessary preliminary to a version. While I do a great many versions, most of them are not prophylactic or elective versions but are to correct abnormalities, chiefly posteriors, occasionally face and brow presentations.

DR. IRVING W. POTTER, BUFFALO, N. Y.—This is not a paper on theory. It is a practical paper upon a practical subject in the field of obstetrics. The writer has had a very extensive experience in the management of cases of version and extraction and from his experience he has made the observations, which he has rounded into a paper. This paper was not on the indications for version, but it was an attempt to point out some of the dangers and pitfalls of a procedure that should be understood and is not understood.

We had many years ago an investigation that would satisfy almost any one. Early papers of mine were discussed, but they refused to print them until they had come to Buffalo and made an investigation. The Health Department looked over our records, and our maternal and fetal mortality were all investigated. I do not know how many times the Health Department called me up and wanted to know if they should let investigators go through the records. I said, "Certainly, we have nothing to conceal."

We have only tried to demonstrate the technique of version, and if you cannot regulate your indications that is not my fault, and if you cannot learn the technique that is not my fault. There is nothing personal about this.

DR. MILTON G. POTTER (closing).—This paper was not on indications for version and extraction and for that reason I will not at this time answer the many questions asked concerning indications. I repeat, this paper only attempted to present the pitfalls one may run into if at any time the operator felt that version was indicated.

THE RELATION OF URETERAL PAIN TO MENSTRUATION

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HUNNER[1] was the first to call attention to ureteral pain due to stricture. The slowness with which this was accepted is undoubtedly due to the fact that pathologic evidence was difficult to obtain, that x-ray studies fail to give concrete information and that in *uninfected* cases, of which there are many, *no abnormal elements are found in the urine.*

The etiology of ureteral stricture is also indefinite, there being some evidence that they are congenital and some that they are due to either focal infection or are a result of urinary infection early in life. Their existence in conjunction with stone leaves a question of which is cause and which is effect. However, those of us who have noted that thorough dilatation of the ureter has been instrumental in preventing recurrent stones feel that the stricture with its resulting stasis is a factor behind the formation of calculi.

Besides stricture, it is also quite likely that spasm of the ureter may cause pain. Wharton[2] has described the manner in which the sympathetic nervous system supplies the ureter and since intestinal and uterine spasm are conceded, it seems reasonable that a similar condition may occur in the ureter. *When we understand more thoroughly the behavior of the sympathetic nervous system we will better understand chronic pain.*

Accepting ureteral stricture and spasm as causes of pelvic pain, there need no longer be a confusion in diagnosis if disease of the appendix, tube, or ovary cannot be demonstrated. In fact, it should be pointed out that the ovary, so frequently accused, rarely causes pain except when it is the seat of an easily demonstrable pathologic condition. Neither is it necessary to have stone, infection, or tumor present in the ureter to produce pain, any more than that there must be some tangible pathology in the uterus to produce dysmenorrhea.

In choosing the following cases I have included only those in which the patient's primary complaint was painful menstruation. In fact, careful questioning was necessary to elicit the character of the pain and separate it from the usual uterine cramps. Let it also be emphasized that the ureter has not been the only obscure cause of pelvic pain. Cervical lesions, as suggested by Young[3] and by Sutherland[4] have also been noted. Patients with unsatisfactory sex life, notably those practicing interruptus coitus, may have, probably due to ovarian congestion, severe lateral pain at the menstrual period with negative pelvic findings.

The symptoms presented by patients suffering from ureteral spasm or stricture may be varied, but the important one is pain. This is similar in its location and radiation to the colic accompanying the passage of a

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22, to 24, 1938.

stone but varies in severity and extent. It is usually described as a "boring pain" or a "dull hard ache" low in the side, and it may begin a week or ten days before the onset of the period and last with varying intensity until the flow is well established, or it may occur only just before or during menstruation. The pain is often referred to the ovary which may be tender to palpation thus leading to errors in diagnosis. Very often too, there is a frequency of urination, erroneously attributed to pressure of the engorged uterus upon the bladder. The presence of burning or pain on voiding depends on whether or not there is an infection.

The physical findings are few. The presence of one or more abdominal scars on a patient who still has the pain originally complained of is excellent indirect evidence that the trouble is in the urinary tract. There are three points of tenderness which lead to the impression that the ureter is at fault: First, the costovertebral angle, second, a point lateral to and below the umbilicus, where the ureter crosses the pelvic brim and a third, the area where the ureter enters the bladder.

The first is variable and its absence in no way eliminates the ureter. The second (Morris's point) where the ureter dips into the pelvis is somewhat more reliable. However, tender loops of bowel or even the anterior aspect of a painful sacroiliac joint may cause soreness at this point. The third region at the vesical end of the ureter, as palpated vaginally, is most important. This is reached by turning the examining fingers to the lateral portion of the anterior vaginal wall where the ureters converge to the trigone. If the ureter is the cause of the pain it should be tender at this point. Since the presence of tender loops of bowel in the pelvis may give false evidence, considerable advantage has been gained by the following procedure: The table is raised to a moderate Trendelenburg position with the head elevated enough for comfort; by a gentle upward stroking of the abdomen the pelvis may be thus freed of coils of intestine.

If gross disease of the pelvic organs has been found, its importance must be properly evaluated since some of these lesions cannot produce pelvic pain of the character described. The surgical removal of diseased structures although perhaps justified may have no effect upon the pain for which the patient has sought relief. The failure to realize that the absence of pus or blood in the urine does not always rule out the existence of ureteral stricture has led to many errors.

The final identification of the ureters as the cause of pain rests on cystoscopic examination. Testing with a bulbed catheter is probably the most satisfactory means of identifying stricture. The obstruction is located by the "hang" of the bulb as the catheter is withdrawn. The one procedure which leads most frequently to error is the relying upon the passing of the No. 6F ureteral catheter. This catheter will find only the most severe stricture or spasm, and negative findings by this method are worthless. In 1923 I[5] described a technique for ureterogram which is of help in locating strictures. Often, however, x-ray reveals no information. The obstruction to bulb or catheter and the identification of the character of the pain are the most reliable points in diagnosis.

In the treatment, gradual dilatation of the ureter up to a 14F or 16F is usually successful. This may be done with a bulbed catheter or a graduated bougie. When the obstruction is in the lower third of the ureter, the bougie works satisfactorily and seems to produce less trauma than the bulb. *In cases of true stricture the patient must be warned that contraction of the lumen may return and occasional future treatments be necessary.*

In cases of severe spasm unrelieved by dilatation, Wharton[6] reports success with an operation for completely denervating the ureter from a point opposite the third lumbar vertebra down to the bladder wall. This procedure gave partial relief in one of my cases and none in another.

From my records I have found 14 cases presenting the complaint of dysmenorrhea in which the pain was lateral and radiated along the course of the ureter. They naturally fall into three groups. In the first there are 3 patients. One, a girl, 15 years old, began to menstruate at the age of 13. Painful periods began one year later. Various remedies had been used and she was referred for cervical dilatation. However, the pain was on the left side and radiated down the inner aspect of the thigh. At cystoscopy a No. 6F catheter was passed easily into the left ureter and produced no pain. A No. 11F Garceau catheter would pass only part way up the ureter, met considerable spasm, and it produced a pain identical with the one complained of. The ureter was dilated three times and all pain disappeared.

The other two patients in this group had pain on the right side and were relieved by dilating the ureter up to a 12F. It seems reasonable to suppose that the underlying cause in these cases was more a spasm than a stricture.

In Group 2 there are 8 cases. In 3 the pain was on the left side only, in 4 on the right, and in 1 it was bilateral. Four admitted some frequency or distress on urination and 4 had none. Three had had 2 operations each for the relief of the menstrual pain without benefit except that in one, "cramps and backache" were improved by a uterine suspension, although the pain in the side was uninfluenced.

The diagnosis of stricture in these cases was based upon obstruction to the ureteral catheter with or without bulb and the reproduction of the pain complained of. No hydronephrosis was found in any of them. Three received dilatation up to 15F, 2 to 14F, and 2 to 16F. In one, an early case, the dilatations were completed elsewhere and I do not know how large a bougie was used.

All reported as completely relieved except one. She was a very nervous and skeptical individual who had had two unsuccessful surgical attempts to relieve her pain. She had a very dense left ureteral obstruction which was dilated to 15F. She had eight months of relief for the first time since the onset of pain, but in spite of warning that she would need further dilatations if the pain returned, she refused treatment when this occurred.

In the third group are three cases which I will report in slightly more detail. The first is a single woman, aged 35 years, seen in January, 1931. Her complaint was severe pain in the lower left side appearing about a week before her period and continuing with increased severity until the flow began. It was aggravated by the presence of intestinal gas. There was also frequency and burning on urination. She had had a "chronic appendix" removed with relief of a right-sided pain. On examination, the pelvic organs were normal but the vesical end of the left ureter was tender and cystoscopy reproduced her pain. At this time as on several other occasions, edema around the ureteral orifices was noted. Many dilatations failed to relieve her. Consultations with internists, neurologists and psychiatrists failed to lead to a more definite diagnosis. Exploratory laparotomy in August, 1932 did not show any gross intra-abdominal pathology. At that time denervation of the left ureter according to Wharton's technique was done. The discovery of an elusive ulcer in 1936 and its treatment with phenol resulted in relief of the bladder distress, but the left-sided pain has never entirely disappeared, although it has been less frequent and less severe since the ureteral denervation.

This patient had numerous symptoms which were not always constant. Pain would occur in one side and again in the other or all symptoms might suddenly improve for no apparent reason. This, plus the fact that edema of the ureteral orifices was seen on several occasions, suggests the possibility that allergy plays a part in her trouble. This fits rather closely with the suggestions of Schwarz[7] and of Goodall[8] that dysmenorrhea in some cases may be due to this phenomenon. As far as I know, her allergy reactions have never been studied.

The second patient in this group was single, aged 24 years. For three years there had been a severe pain that radiated from the right kidney region along the entire course of the ureter. It appeared ten days before menstruation and lasted throughout the period. She had had the appendix removed without relief. On examination the pelvic organs were normal. The right kidney and ureter were tender. The ureteral catheter met marked obstruction and reproduced the pain. Dilatations up to 16F failed to give relief. Complete physical and mental survey by all departments failed to lead to a more definite diagnosis. A thorough exploratory laparotomy disclosed grossly normal abdominal and pelvic organs. Bilateral ureteral denervation was done. This likewise gave no relief. Besides these procedures the patient had received various hormone therapy without result. At my request the patient returned recently, stating that in March, 1938, she had been operated upon in another city, with relief of her pain. A report from the surgeon stated that after careful study, presacral neurectomy had been done but that the patient had told him she was not completely relieved.

This patient is particularly interesting. If the pain was of ureteral origin as its character seemed to indicate and *any* form of sympathectomy would relieve it, it would seem that complete ureteral denervation should have given at least a temporary good result. Since presacral neurectomy has been followed by marked improvement, it must be assumed that the ureter itself was not the cause of pain.

The third patient in this group, single, aged 27 years, was first seen in August, 1934. She had complained of severe dysmenorrhea with the usual uterine cramps accompanied by a persistent pain in the lower left side seemingly along the course of the ureter. She had had several operations resulting in the loss of her right ovary, appendix, and part of her left ovary. A suspension of the uterus and several dilatations of the cervix had been done and no relief was obtained. Catheterization of the left ureter failed to identify the patient's pain. However, its character seemed so typical that several ureteral dilatations were done but failed to cause improvement. Presacral neurectomy was followed by relief of the uterine cramps but the pain in the left side has persisted. It is very doubtful that the pain in this case was ureteral in origin. It would have been very interesting to have studied her before the function of her pelvic organs had been disturbed by so many operations.

COMMENT

The records of 14 patients whose chief complaint was painful menstruation have been presented. In each the pain differed from that of typical dysmenorrhea by occurring in the side and radiating along the course of the ureter. In 11, the fact that dilatation of the ureter resulted in relief indicates that the pain did originate in that organ. In 3 cases symptoms, although seemingly related to the ureter, failed to be influenced by dilatation. One of these was partially benefited by denervation. This patient also presented some evidence that allergy may play a part in her distress. One patient has obtained at least temporary relief from presacral neurectomy.

CONCLUSION

There are certain cases of dysmenorrhea in which the pain has an obscure and unusual origin. These require the most painstaking study, often needing the combined efforts of many branches of medicine. This should be recognized and surgery withheld until some definite procedure can be outlined.

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DISCUSSION

DR. HENRY D. FURNISS, New York City.—Ureteral stricture is a real condition, but it took the gynecologists a long time to convince the rest of the profession that this was so. The first one I discovered was by accident, in a patient who had previously been operated upon for a gall bladder condition. During her convalescence she had exactly the same type of attack for which the operation had been performed. Observation of a relationship between the pain of stricture and the menstrual period was made fifty years ago by Mirabeau. Whether the condition is due to some hormonal action or to ureteral congestion, I do not know.

Unexpected results have followed the dilatation of some of the strictures. One patient, for example, was freed of a diarrhea of several weeks' duration. Hunner has stressed this point and has reported relief of so many symptoms, seemingly entirely unrelated, that many are still skeptical. My experience has proved him to be right.

How these strictures form I do not know. We find ureteral orifices that are small and in no way the result of previous disease, so we must consider these of congenital origin. I believe that many strictures are due to an old cystoureteropyelitis, with subsequent narrowing of the ureter. The pyelitis may have been due to a congenital stricture of the ureter, as substantiated by the work of Meredith Campbell. At times, it is impossible to prove a stricture by either retrograde or intravenous urograms; yet the patient is relieved by ureter dilatation.

DR. W. A. COVENTRY, Duluth, Minn.—I would like to ask Dr. Sears if he can explain why these patients have pain immediately before menses and then after menstruation the pain ceases, and also whether these patients have any symptoms except during the time they are menstruating.

DR. J. P. PRATT, Detroit, Mich.—It is gratifying to hear Dr. Sears refer to the psychiatric aspects of ureteral and pelvic pain. He has indicated that spasm of the ureter is frequently responsible for the pain. What is the explanation of the spasticity? Definite organic causes are often easily demonstrated. More often, however, the cause of spasm is elusive. Stone, inflammation and tumor are definite terms readily understood. Emotional disturbance is not so easy to define but is no less potent as a cause of ureteral pain.

DR. SEARS (closing).—Dr. Furniss' experience with ureteral pain has been extensive, and I am pleased to have him join me in the plea for earlier recognition of this condition.

The only answer I have to Dr. Coventry's question is that through the sympathetic nervous system the hormonal changes in the blood at this time affect the ureteral muscle as they do that of the uterus. Ureteral pain, of course, may occur at any time, but I have chosen to report only the pains occurring in relation to menstruation.

I want, especially, to thank Dr. Pratt for emphasizing the psychogenic factor in pain, a point which I had time only to mention.

Any patient complaining of pain for which there is not an evident pathologic explanation, requires the most careful investigation. Some will be relieved by ureteral dilatation, some by very careful psychiatric investigation, and some by correction of cervical lesions. In some, sympathectomy will be followed by relief. Although this procedure is entirely justified at the present time, I believe the future will show that it will be possible to correct the condition which produces this spasm rather than dividing the nerves which carry the impulses.

BENIGN TUMORS OF THE CERVICAL STUMP FOLLOWING SUPRAVAGINAL HYSTERECTOMY*

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FIBROMYOMA of the cervical stump following supravaginal hysterectomy constitutes one of the unusual varieties of benign neoplasms. It occurs even less frequently than myoma of the vaginal portion of the cervix in intact uteri, which is also an uncommon condition. Much has been written on the subject of malignant tumors following operation, but since the first case of fibroma of the cervix was reported by Giles in 1923, only six additional case reports have appeared in the literature. The gynecologist apparently rarely encounters this condition, and it is only from the larger clinics that an occasional case is reported. In over 1,800 supravaginal hysterectomies performed at the New York Post-Graduate Hospital in the last eight years, but two cases of true fibroma of the cervical stump were found by other operators. These two, with two personal cases, form the basis of this presentation.

CASE 1.—Mrs. A. S., aged 49 years, was first seen by me in August, 1937, at which time she complained of pain in the right side of the abdomen and excessive flatulence of several years' duration. She gave a history of cholecystectomy and appendectomy sixteen years previously; both breasts had been removed for tumors; one five and one-half years, and one three years previously. Five years before, supravaginal hysterectomy, with prophylactic attention to the cervix, had been performed for uterine fibroids. The pathologic report of each of the tumors revealed no evidence of malignancy. Physical examination was essentially negative except for the four scars from the previous operations, one at the site of each breast amputation, and two on the abdomen. The cervix, however, was markedly eroded, hypertrophied, and bled easily when lightly traumatized. There were no palpable tumor masses. An immediate biopsy of the cervix showed chronic endocervicitis with no evidence of malignancy. The patient was advised to have the cervix removed as a prophylactic measure. She did not return for this, and was seen at irregular intervals up to March, 1938, at which time she had a severe vaginal hemorrhage. At the onset of bleeding, she was taken to an out of town hospital near her home, where treatment failed to control the bleeding. Four days later she was transferred to New York. When I saw her then, she appeared markedly anemic and somewhat exsanguinated. The cervix was very much enlarged, but the external os could not be identified. The bleeding seemed to come from the right lateral posterior aspect of the cervix, although the exact site could not be definitely determined. On bimanual examination, a tumor mass was found extending from the cervix into the pelvis, approximately the size of a large grapefruit. Because of the position of the tumor and the condition of the patient, it was felt that deep x-ray therapy might be beneficial. The roentgenologist, however, did not concur in this opinion. The patient was given several blood transfusions and treated conservatively, with a view to improving her general condition before operation. One month later, she again had a profuse vaginal hemorrhage. There was no change in size or consistency of the tumor mass, and again, the external os of the cervix could not be located, so the patient was prepared for operation. On opening the abdomen, widespread, dense adhe-

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 22 to 24, 1938.

sions were found between the omentum, small intestines, and the tumor mass. The corpus of the uterus, ovaries, and tubes had evidently been removed at a previous operation. On freeing the adhesions, a tumor mass, the size of a large grapefruit was found originating in the cervical stump, extending downward into the cul-de-sac and recto-vaginal septum. The tumor was enucleated without difficulty, and the cavity tightly packed to control persistent oozing. Following the operation, a blood transfusion of 500 c.c. was given. Her progress was satisfactory up to the fifth day when she developed a left parotitis. Two x-ray treatments were given for this and the rest of her convalescence was uneventful. The tumor measured 10 by 9 by 7.5 cm., and was encapsulated by a tough fibrous membrane through which many dilated vessels were seen; on section, it was of firm consistency and pearly white in color. It was composed of interlacing bundles of smooth muscle fibers and fibroblasts between which were bundles of collagenous fibrous tissue. There were no areas of hemorrhage or degeneration.

CASE 2.—Mrs. A. D., aged 42 years, was first seen by me in June, 1932, at which time a supravaginal hysterectomy with retention of both tubes and ovaries was done for multiple uterine fibroids. At that time, the uterus was amputated just below the internal os by making a wedge-shaped excision, the cervix coned out from above, and touched with carbolic acid followed by alcohol. The pathologic findings were multiple intramural fibromyomas of the uterus with hyaline degeneration and chronic polypoid endometritis. The patient was well until March, 1937, at which time she complained of marked constipation, pain in the lower abdomen, and vaginal discharge of six months' duration. On pelvic examination, a hard mass, the size of a hen's egg which seemed to be attached to the stump of the cervix was palpated; it had the consistency of a solid tumor. At operation, a tumor mass was found extending into the right broad ligament, the pedicle being attached to the stump of the cervix. Except for considerable bleeding, it was removed without difficulty, and the patient made an uneventful recovery. On histopathologic examination, the tumor was found to be a leiomyofibroma.

CASE 3.—(Patient of Dr. Walter T. Dannreuther.) Mrs. M. M., aged 39 years, complained of vaginal discharge, pain in the left side of the abdomen and slight vaginal bleeding for the past year. Four previous abdominal operations had been performed, but the patient did not know what had been done. She had not menstruated since the first operation. She had previously had 4 children and several induced abortions. Examination revealed the presence of several tumor masses just above the cervix extending into the right iliac fossa. On opening the abdomen, dense adhesions were found and a group of tumors which had evidently grown in the cervical stump were demonstrated; both tubes and ovaries which had not been removed at any of the previous operations were removed with the fibromyomatous mass.

CASE 4.—(Patient of Dr. Thomas Cherry.) Mrs. R. G., aged 50 years, complained of vaginal bleeding for six weeks. A hysterectomy had been performed three and one-half years previously. Her menstrual periods had continued regularly for one year, but were of but one or two days' duration, and then ceased entirely. Six weeks previous to examination, she noted spotting, and complained of mild pain in the right flank, frequency of urination, urgency and partial incontinence. At operation, dense adhesions were encountered and a tumor mass 11 cm. in diameter, deep in the pelvis, originating from the stump of the cervix was found. This was adherent to the bladder, which had been pushed upward with the growth of the tumor. The pathologic examination showed a fibromyoma of the cervix with hyaline degeneration.

REVIEW OF REPORTED CASES

The first recorded case of benign tumor of the cervical stump is that of Giles in 1923, who referred to an unpublished case of Bruce-Porter. He removed a large fibromyoma from the cervical stump, five years after a subtotal hysterectomy for multiple fibroids, in a woman 39 years old. The condition was unique in his experience although he had performed nearly 1,000 hysterectomies, most of which were subtotal.

The following year, Reder reported a third case, one of myoma of the posterior cervical lip which was found three years after supravaginal amputation of the corpus.

Cleland's case was designated by him as a mucocele of the cervical stump, occurring fourteen years after supravaginal hysterectomy with removal of both tubes and ovaries for leiomyomas of the uterus; the cervix was in good condition at the time of the first operation. He was unable to give it a better name than cystic degeneration of the cervical stump.

Moench's case, reported in 1929, was of particular interest in that it was found six weeks following hysterectomy.

The largest benign growth was reported by Fletcher in 1935. Eight years after hysterectomy, he removed a fibroid from the cervical stump, weighing 12½ pounds, apparently subvesical in type.

Greenhill's case was also subvesical and the interval between the hysterectomy and the discovery of the tumor was the longest on record, seventeen years. The growth was entirely covered by the bladder on its anterior and posterior surfaces.

COMMENT

It is apparent that benign tumors of the cervical stump are predominantly fibroma. Histopathologic examination shows that their structure is essentially the same as those of the uterus or cervix. There are no demonstrable causes for fibromyomas, and some of the theories which have been advanced concerning their origin are open to serious question, especially in the light of certain factors present when they develop in a cervical stump. It has been contended that excessive ovarian activity causes a hyperplasia of the uterine muscle cells in local cellular areas with impaired circulation, but in many cases, hysterectomy and removal of the endometrial tissue had been performed several years before the appearance of the cervical tumor. Another theory has been that menstrual blood is forced back by a retrograde current, irritating the tissues and causing proliferative action. This is hardly tenable because many of these patients did not menstruate after the operation. The interval between the last menstrual period and the discovery of the tumor varied from six weeks to seventeen years.

Fibromyomas of the corpus are frequently multiple, but those of the cervix are usually single. A review of all of the available cases of those of the cervical stump reveals but one instance of multiple tumors. It is certain that tiny tumors may be overlooked and left in the tissue after fundal amputation. All of us have seen them and removed those which were macroscopically evident. It is interesting to speculate as to their outcome. Most must remain quiescent, in view of the small percentage developing in the cervical stump when so many hysterectomies are performed for fibroma of the uterus. Is it possible that one of these tiny tumors left in situ increases to such size as to necessitate operative intervention? And how can we account for the growth of but one?

There has been some diversity of opinion regarding the need of prophylactic treatment of the cervix at the time of hysterectomy, but the majority of surgeons advocate removal or destruction of the endocervical and endometrial tissue and glandular structures by excision, cauterization, or the application of high frequency current or chemical corrosives. Some adhere to a "leave alone" policy, whether the ovaries are removed or not. Others feel that an adequate amount of endo-

metrial tissue acts as a stimulus for normal glandular function when the ovaries are not removed. Is it possible that the eradication of this focus may account for the low percentage of tumors, benign or malignant, occurring in the stump? If this be so, how can we account for the fact that they do occur when prophylactic measures have been taken?

These tumors apparently grow more rapidly than those of the body of the uterus and may attain a considerable size. The majority originate in the posterior portion of the cervical stump and tend to grow backwards toward the cul-de-sac. They may be retroperitoneal, intraligamentary, or subvesical.

The first manifestations are usually obstructive, due to pressure of the growth—marked constipation, pain in the abdomen or pelvis, and if adhesions are present, drag on the adjacent viscera. With pressure on the bladder, the patient complains of urinary disturbance, urinary frequency, urgency, incontinence, or retention. Vaginal bleeding or discharge is frequently present; it may be slight or profuse. In one of our patients, the bleeding was so severe that immediate transfusion was necessary.

If the possibility of such a tumor is borne in mind, the diagnosis should not be difficult. It is based on palpation of a solid tumor attached to or in relation to the cervical stump. If the mass fills the pelvis, there may be some confusion as to the origin and type of tumor, particularly if the uterine adnexa have not been removed or dense adhesions are present. Due to the location of the growth and possible distortion of the ureters or bladder, a careful urographic study of the urinary tract should be made to determine the relation of these structures to the tumor before treatment is instituted.

Surgical intervention should be prompt. Because of the site of the growth and its tendency to grow upward and backward, the abdominal route offers the best method of approach. The operation may be difficult and tax the skill of the surgeon, as dense adhesions usually present may cause malposition, distortion or fixation of the adjacent structures. Once free, the tumor is easily shelled out. The possibility of distortion of the bladder from a previous operation or possible atypical position of the ureters should not be overlooked, and care must be taken in the identification, separation, and preservation of these structures. If the tumor mass is found so adherent to the bladder that separation cannot be accomplished without injury to the viscus, it is advisable to resect that portion of the bladder with the tumor mass, and repair the opening in the bladder wall. There is usually considerable venous oozing from the cavity from which the tumor is enucleated and this is best controlled by packing. All raw areas should be peritonized. It is gratifying to note that all of these patients recovered, despite the poor physical condition of some of them.

Our present knowledge does not permit of a logical explanation for the spontaneous development of these tumors, and it is only by a study of a much larger group of cases than is now available, that the true cause may be determined.

SUMMARY AND CONCLUSIONS

1. Benign tumors of the cervical stump are extremely rare.
2. Four new cases are presented, with a review of the literature.
3. Some of the etiologic explanations advanced for the cause of tumors of the uterus or cervix are obviously incorrect.
4. It is only by the study of a much larger group of cases than those now available that further light will be thrown on this subject.
5. The possibility of a benign cervical tumor should be borne in mind.
6. Early surgical removal is advised.

I wish to thank Drs. Dannreuther and Cherry for their courtesy in permitting me to report their cases.

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DISCUSSION

DR. LOUIS E. PHANEUF, Boston, Mass.—Dr. Hyams has brought to our attention what appears to be a very rare gynecologic condition. I, personally, have performed very close to 1,000 hysterectomies, a high percentage of which were supravaginal, and have not met this lesion, nor have I seen it listed in the records of the Carney Hospital for the past twenty-five years.

Dr. Hyams' case reports reveal an important fact, and that is that these neoplasms are handled better abdominally than they are vaginally. The close proximity of these tumors to the ureters and bladder, to which they may be adherent, would make the vaginal operation arduous and difficult in many instance, whereas by working abdominally, as has been pointed out, the danger of injury to these structures is greatly lessened.

DR. HENRY SCHMITZ, Chicago, Ill.—A review of our clinical records did not show a single instance of myoma in a cervical stump. The incidence of cervical location in uterine myomas is 8 per cent. However, the incidence of carcinoma in the cervical stump is 2.5 per cent in about 1,000 cases of cervical cancers.

In the first case reported by Dr. Hyams the patient, according to the report, was seen first in August, 1937, when a cervicitis was found. About seven months later, i.e., March, 1938, on readmission for severe hemorrhages, a tumor mass the size of a grapefruit was present extending upward to the right of the cervix. The histologic findings were those of a leiomyofibroma. I wonder whether microscopic re-examination of the tissue might not show the presence of large, atypical cells stamping the tumor a sarcoma, or the formation of numerous round cells dispersed within the myoma indicating a morphologic transition to sarcomatous degeneration, the so-called myoma malignum. Only thus could be explained the hemorrhages and the rapid growth.

It may be said that tumors appearing within one year after the operation were probably present at the time of operation. Moench reported such a tumor 11 cm. in diameter within six weeks after a subtotal hysterectomy.

The rarity of such tumors therefore should not contribute another factor to the controversy of total versus subtotal hysterectomy, if the cervix is normal at the time of operation. Such tumors should not be treated with radium or roentgen rays as they are invariably associated with pain either from pressure or inflammation.

DR WALTER T. DANNREUTHER, NEW YORK CITY.—I now have under observation two additional cases. One is a woman operated upon by myself sixteen years ago, in whom I did a high fundal amputation without coning out the cervical stump, and in whom I succeeded in preserving a miniature menstruation, which was important for psychologic reasons. About a year ago this patient returned complaining of symptoms other than those relative to the cervical stump, and I then found that she had a hard, round and symmetrical tumor, about the size of a hen's egg, involving the entire cervix. It is causing no local symptoms, and since she is now 49 years of age, I anticipate that with the onset of her menopause there may be a regression of the new tumor.

A second patient was operated upon five years previously by someone else, and in this instance there was no reason to attribute the symptoms, for which she consulted me, to a cervical tumor, despite the fact that such a tumor was quite evident. As this woman is also close to the climacteric period, and in view of the fact that the tumor is symptomless, I have not urged another operation. I can therefore include in my own experience not only the case cited by Dr. Hyams, but also two additional ones. The point I might emphasize is that there are cases of postoperative fibroid tumors of the cervix which do not produce either leucorrhea or hemorrhage.

DR. WILLIAM H. WEIR, CLEVELAND, OHIO.—An interesting condition was found recently in a young woman who had complained for two years of severe pelvic pain, lasting for two weeks of each month at the time of the period. This pain had not been relieved by supravaginal hysterectomy eight months previously. On examination a tumor about an inch in diameter and exquisitely tender to the touch was found to the right of the cervical stump and apparently adherent to it as well as to the base of the bladder. The surgeon who performed the hysterectomy said that the tumor was apparently not there when he operated. For this reason, and owing to the extreme tenderness of the mass, the possibility of its being an ovary adherent to the cervical stump was considered. However, an endometrioma seemed the most probable diagnosis. The tumor, together with the cervix, was removed through an abdominal incision. It was so intimately connected with the bladder that the two had to be separated by sharp dissection and a small tear in the bladder wall resulted. This was repaired but a tiny vesicovaginal fistula persisted. However, this was successfully closed from below a few weeks later. The tumor on section showed the typical gross and microscopic appearances of an endometrioma with small black hemorrhagic areas throughout it, and it was quite similar to one about the same size removed a few weeks later from the abdominal scar of a former cesarean section. A question arose whether this should be considered an adenofibroma of the cervix, since the two were so intimately connected, or an endometrioma that had happened to develop in close proximity to the cervix. The gland structure in the tumor being more of the corpus type, it was considered to be an endometrioma.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—I have seen four cases of tumors of the cervix, not all of them, however, occurring after the body of the uterus had been removed. One of them was a low-grade myosarcoma, another was a very rapidly growing sarcoma in the cervical stump. In the latter patient, who had had a hysterectomy for fibroids, the specimen had not been examined histologically but had been preserved, and later when sections were made, it was found that the original tumor was also sarcoma. The other two cases were benign.

DR. HYAMS (closing).—I agree with Dr. Schmitz, that in the first of my personal cases, the rapidity of growth of the neoplasm was highly suggestive of malignancy. With this possibility in mind, I was not content with the first pathologic report, and had the slides and specimens examined by a second pathologist.

Referring to Dr. Dannreuther's case, it is interesting to note that it was the only one in the entire series in which there were multiple fibroids.

INVERSION OF THE UTERUS WITH REPEATED HEMORRHAGES AND REPLACEMENT BY THE USE OF THE AVELING REPOSITOR*

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MRS. H. G., born in the United States, 19 years old, height 5 feet 3½ inches, weight 113 pounds. A blonde, pale young woman whose past history was negative.

She first reported to the prenatal clinic Oct. 5, 1936. Her last menstrual period was Aug. 20, 1936, her expected date May 27, 1937. Pregnancy was normal up to March 6, when she developed a mild pyelitis. She was admitted to the hospital and a culture of the urine showed *Staphylococcus albus*. The red cell count was 3,400,000, the hemoglobin 65 per cent, the white cell count 7,500. She was discharged after a three-day stay in the hospital. She reported regularly to the prenatal clinic and was admitted in labor on May 24.

After a labor of twenty hours she was delivered by low forceps because of a persistent occipitoposterior position. A left mediolateral episiotomy was repaired. There was a moderate amount of bleeding and the placenta was delivered spontaneously after a third stage of twenty-one minutes. This was followed immedi-

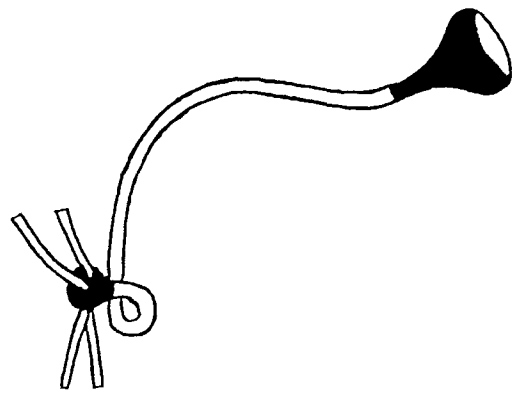


Fig. 1.

ately by a large amount of bleeding estimated at 1,000 c.c.; for this the lower uterine segment and vagina were packed. The cervix was examined and no laceration found, thirty minutes later the patient went into shock, acacia solution and two transfusions were given in rapid succession with little effect.

The patient was put on the table again, at which time a complete inversion of the uterus was discovered. This could not be replaced easily so the vagina was packed tightly with iodoform gauze, which stopped the bleeding. In the ensuing eight hours 1,100 c.c. more of blood were given, making a total of 2,200 c.c., since the delivery of the patient.

On May 29, five days after the inversion, under cyclopropane anesthesia, an attempt at reduction of the inversion was made with no success. Periodic bleeding resembling menstruation developed, and she was never in a condition where operation could be considered. The patient was several times on the danger list and, except for continued transfusions, would probably have died. In addition to this she ran a septic temperature for a long time. Of the many operative measures for her

*Read at the Fifty-First Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, held at White Sulphur Springs, W. Va., September 22 to 24, 1938.

relief, such as Spinelli's operation, replacement by operation through the abdomen or vaginal hysterectomy, none could be considered because of the serious condition of the patient.

Reported series of cases treated with the Aveling repositor showed no mortality; it seemed that this method was at least worth a trial. This instrument could not be obtained from any of the surgical supply houses and the one used in this case was improvised from a pessary used for third degree procidentia. On September 6, or over three months after the inversion, the cup of the repositor was placed against the fundus of the uterus, upward and inward pressure was instituted by the use of four pieces of rubber tubing attached to the stem of the repositor and in turn to a belt about the patient's pelvis. On September 7 the patient had a chill and a temperature of 102.6° F., and on September 8 her temperature was 104°; there was a foul vaginal discharge. It was noted that the sigmoid stem was at a distinctly different angle and had shortened, there was a corresponding laxness of the rubber tubes, the fundus of the uterus with its retained repositor cup was felt through the abdominal wall at the level of the umbilicus. A vaginal examination disclosed the uterus reinverted and the cervix grasping the stem of the repositor tightly. Traction over a pulley on the foot of the bed with a one-pound weight was put on the stem, and the repositor came out about five hours later.

The patient was discharged on December 22, after a hospital residence of 212 days. The delay in her recovery after reposition of the uterus was due, in part, to slow healing of a sacral ulcer and also to her inability to walk because of long confinement in bed.

I believe that this case should be reported for two reasons: first, to demonstrate the absolute necessity, in cases of severe hemorrhage, for massive transfusions (2,200 c.c. in twenty hours); second, to call attention to the value of a simple procedure which is free from serious consequences and which may obviate the necessity for operating on cases of inversion of the uterus, which have resisted simple replacement, namely, the use of the Aveling repositor, which while it may not effect replacement in all cases, nevertheless, is worth a trial. There is no mortality due to its use. Furthermore, it leaves the uterus intact for future childbearing. All of the operative procedures have a definite and not inconsiderate primary mortality.

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26 South Goodman Street

THE EFFECT OF ESTROGENIC HORMONE ON THE H-ION CONCENTRATION AND THE BACTERIAL CONTENT OF THE HUMAN VAGINA, WITH SPECIAL REFERENCE TO THE DÖDERLEIN BACILLUS*

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SINCE the discovery by Döderlein (1892) of the gram-positive, non-sporing, acid-tolerating bacillus which frequently inhabits the vaginal tract of individuals of all ages, much attention has been focused on this organism, first, with respect to the rôle which it has been assumed to play in resistance to infection in the female genitalia by reason of its antibiotic properties, and second, as a therapeutic agent, since, when introduced into the vagina in a suitable menstruum, it was found able to grow and produce sufficient acid to inhibit the other common bacterial inhabitants of this organ. Much controversy has arisen among workers in the field as to the exact part which this organism plays in the production of acidity in the vagina. Döderlein assumed that it is responsible for practically all of the acid present. Many workers since Döderlein have gathered data which indicate a definite correlation between low pH of the vaginal secretions and large numbers of the Döderlein organism present in them. There have been others, however, who have thrown some doubt on the importance of this bacillus in the production of acidity, claiming that it could not attack the carbohydrate, glycogen, occurring normally in the vaginal mucosa.

It has been shown by many that there is a change in the H-ion concentration of the vaginal secretions with alteration in the ovarian activity of the individual. Thus, before puberty the pH ranges between 6.8 and 7.2 and the Döderlein bacillus is present in only a small number of the members of this group. During adult life, while the ovaries are actively functioning, the pH is lower and the aciduric bacillus is present with greater frequency than at the younger age. The Döderlein bacillus is present in 60 to 70 per cent of gravid individuals, the pH being markedly depressed, often reaching a level as low as pH 4.0 to 4.2.

While many have shown that this relationship exists, it could be arrived at only indirectly by inference that this correlation depends on the function of the ovary. It remained for Miura (1928) to furnish the first direct proof that the glycogen of the mucosa, the bacterial flora of the vagina, and the H-ion concentration were dependent on the activity of the ovaries. He studied the vaginal secretions of a number of individuals before and after ovariectomy, and was able to show that while a low pH and large numbers of the Döderlein organism were present be-

*Thanks are accorded Parke, Davis and Company for generous aid in supplying theelin for use in this work.

fore operation, this condition was completely reversed after removal of the ovaries, a change which was accompanied by the disappearance of glycogen from the vaginal mucosa. Cruickshank and his co-workers (1934) and the German school are in complete agreement with Miura's observations that the Döderlein bacillus is the most important agent for the production of acidity in the vagina, although they assume that some nonbacterial agent capable of breaking down the glycogen of the vagina into acid must exist.

Although no one can doubt the close relationship between ovarian secretion, the state of glycogen deposition in the vaginal mucosa, and the H-ion concentration of the secretions, some doubt has been cast on the mechanism of production of the acidity.

Schroeder and others (1926), and Miura and others have shown that the vaginal bacillus cannot break down glycogen to acid in the test tube. Kienlin (1926) demonstrated that appreciable quantities of lactic acid are present in the secretions of the vaginal tracts of newborn infants before any bacteria have as yet invaded the organ. This evidence points to the presence of some other agency in the vagina which is capable of producing large amounts of acid from glycogen, and serves to cast some doubt on the Döderlein bacillus as the most important agent in the production of the low pH levels which may be found.

It was the purpose of the work reported here to attempt to induce a high H-ion concentration in the vaginal secretions of human subjects and to study the bacterial content of this organ while the changes in pH were taking place. Since it has been shown by Hall and Lewis (1936) in monkeys, and by Lewis and Weinstein (1936) in children, that the parenteral administration of estrogenic hormone increases the H-ion concentration of vaginal secretions, human subjects were treated with this substance, and the changes taking place noted. Individuals in the postclimacterium who lacked Döderlein bacilli in the vaginal tract, and in whom the H-ion concentration was about pH 6.8 to 7.2 were chosen as subjects for the experiment.

MATERIALS AND METHODS

A complete history was obtained in each instance, and only individuals lacking evident disease of the genital organs were included in the study. Three observations were made in each case at weekly intervals before treatment was started, cultures and H-ion determinations of the vaginal secretions being made. One specimen of the vaginal mucosa for histologic study was obtained from every patient before the experiments were started. The estrogenic hormone was injected once a week in three consecutive doses; it was given in oil, 10,000 I.U. in each dose.

With the patient in the lithotomy position, a sterile speculum was inserted into the vagina and some of the secretion drawn up into a small pipette capped with a rubber bulb. In many instances, before injection of the hormone was started, there was a marked paucity of vaginal secretion; in such instances, the vagina was washed out with a very small amount of sterile saline solution (about 1.0 c.c.) and H-ion determination was carried out on this material. The pH was determined by the use of colorimetric indicators: bromthymol blue for the range 6.0 to 7.6, bromcresol purple for the limits 5.2 to 6.8., and bromcresol green for the range 3.8 to 5.4. Although this method of carrying out pH determinations is open to criticism on the ground that it is not accurate within 0.2 of pH unit, the changes which were considered significant were always of a much greater magnitude, and any error in the

method was thus reduced to a minimum. Furthermore, since the same method was always used, figures which were significant from a comparative standpoint were obtained, any inherent error in the method being constant.

The cultures of the secretions were made by swabbing the vaginal walls with a pair of sterile cotton swabs, immersing these in sterile saline solution and culturing within two hours on the tomato-yeast-peptonized milk medium of Weinstein, Weiss, Rettger and Levy (1933). This medium had previously been shown to be very efficient in growing organisms of the Döderlein type, endowing them with a colonial morphology (rough, fuzzy colonies) which made their recognition in a pour plate very simple. All cultures were incubated at 37° C. in an atmosphere of carbon dioxide and air for forty-eight hours, and then examined for the typical colonies, counts being made wherever the Döderlein organism was present to determine the relative frequency of this organism, as compared to the other bacteria in the vaginal secretions.

Sections from the vaginal mucosa were taken once a month for histologic study. These were fixed in formalin, stained according to the conventional methods, and then examined to determine the stage of development of the vaginal mucosa as a check on the effect of the hormone, and in an attempt to correlate these data with the findings of the cultural and pH determinations.

Cultures and pH readings were made for three weeks before the injection of hormone was started and every week after the beginning of the therapy, wherever this could be done. In some instances weekly specimens were not obtainable, but determinations were carried out with great enough frequency to make the results obtained significant.

RESULTS

As can be seen from Table I, the pH, which in every case was close to 7.0 at the outset, fell shortly after administration of the hormone to fairly low levels. In one case only was there no appreciable increase in H-ion concentration following the injection of the estrogenic substance; this individual (Case 7) had been subjected to ovariectomy and had been receiving hormone for one year prior to this study. All of the other individuals were in the natural postclimacterium and had not been treated previously. The average decrease in pH following the injection of 10,000 I.U. of the hormone was one pH unit. Further injections reduced this level still lower in most cases, pH 5.0 being not unusual. In several instances H-ion concentrations of pH 3.8 to 4.8 were observed. The findings in these individuals substantiate the results obtained by Hall and Lewis in monkeys, and by Lewis and Weinstein in young children following administration of the estrogenic hormone.

Following cessation of treatment, the pH tended to remain low in most instances: it returned slowly in some cases to a level closely approximating that present before treatment was started. In some individuals the H-ion concentration did not return to that observed before the experiment was begun. No explanation for this phenomenon is at hand.

The table indicates clearly that in 7 of the 9 individuals studied, the Döderlein bacillus was not present in detectable numbers during any part of the investigation. In spite of the fact that the vaginal secretions became very acid, this organism, which has been thought to be responsible for much of the acid in the vaginal secretions, could not be demonstrated.

Two of the patients harbored the Döderlein bacillus during the course of this investigation. In Case 6 it was present at pH 6.8, and at pH 5.8 to about the same extent. Later in the study, this bacillus was not present at pH levels as low as 5.0. There seemed to be little if any correlation between the degree of acidity and the presence of the vaginal bacillus in this individual. This observation receives further emphasis when Case 7 is considered. Here, large numbers of the aciduric organism were present in the vaginal secretion when the H-ion concentration approached the neutral point or even slightly exceeded pH 7.0 (pH 6.8 and pH 7.2). In fact, in this individual the organism could be detected at one time at a certain pH level, and one week later could *not* be demonstrated in the secretions of the same H-ion concentration.

TABLE I. H-ION CONCENTRATION AND DÖDERLEIN BACILLUS CONTENT OF VAGINAL SECRETIONS OF INDIVIDUALS TREATED WITH ESTROGENIC HORMONE

DATE	CASE 1		CASE 2		CASE 3		CASE 4		CASE 5		CASE 6		CASE 7		CASE 8		CASE 9	
	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.	pH	% DÖD.
1/11	7.2	0	6.8	0	7.0	0	6.8	0	7.0	0	7.0	95	7.2	60	6.8	0	7.0	0
1/18	7.0	0	6.8	0	7.2	0	7.0	0	6.8	0	6.8	90	7.0	30	7.0	0	7.2	0
1/25	7.2	0	6.6	0	7.0	0	7.0	0	6.8	0	7.0	70	7.0	0	6.8	0	6.8	0
2/1	7.2*	0	6.6*	0	6.8*	0	6.8*	0	6.8*	0	6.8*	95	7.0*	90	7.0*	0	6.8*	0
2/8	6.0*	0	5.6*	0	6.6*	0	–	–	–	–	5.8	95	–	–	6.2*	0	5.6*	0
2/15	6.0*	0	5.6*	0	5.2*	0	7.2*	0	6.8	0	5.8*	95	7.2*	10	5.6*	0	5.0*	0
2/25	5.8	0	5.0	0	6.0	0	6.0*	0	7.0*	0	–	–	6.8*	95	5.0	0	5.2	0
3/1	5.0	0	4.8	0	–	–	4.8*	0	5.4*	0	5.8*	0	6.6*	0	4.6	0	5.0	0
3/8	6.8	0	5.8	0	4.8	0	3.8	0	3.8*	0	–	–	–	–	5.2	–	5.6	0
3/15	7.2	0	5.2	0	6.0	0	5.4	0	–	–	6.0	–	–	–	5.6	0	–	–
3/22	7.2	0	5.0	0	6.2	0	5.8	0	5.0	0	Menses	–	7.0	0	5.2	0	6.0	0
3/29	6.8	0	5.0	0	5.0	0	6.0	0	4.8	0	–	–	7.2	0	–	–	–	–
4/5	7.0	0	5.8	0	5.0	0	6.6	0	5.4	0	–	–	7.2	0	6.0	0	6.2	0
4/19	7.2	0	5.8	0	–	–	5.4	0	5.2	0	6.2	95	6.8	0	–	–	–	–
5/3	7.2	0	–	–	5.4	0	6.8	0	–	–	5.0	0	6.8	0	–	–	6.8	0
6/7	7.2	0	–	–	5.6	0	6.0	0	–	–	6.6	0	7.2	0	6.6	0	6.4	0
6/28	7.2	0	5.6	0	6.0	0	–	–	5.8	0	6.8	90	7.0	0	6.8	0	6.6	0

*10,000 I.U. of theelin injected intramuscularly.

Histologic study of the vaginal mucosa before and after treatment with the estrogenic hormone showed a definite correlation between the appearance of the tissue and the H-ion concentration of the secretions. Before treatment was started the pH was close to the neutral point and the mucosa was thin and revealed no evidence of active growth. Following administration of the estrogenic hormone, growth of the mucosa occurred with a corresponding increase in H-ion concentration. Sections taken at low pH levels showed many layers, and strong evidence of activity of the stroma. With cessation of treatment and a return of the H-ion concentration toward the neutral point, the vaginal mucosa again became thin and resembled that found before the experiments were begun.

SUMMARY AND DISCUSSION

Estrogenic hormone administered parenterally is capable of increasing the acidity of the vaginal secretions in cases where the pH is close to the neutral point before treatment. This change can be brought about *without* the intervention of the Döderlein bacillus, a fact which seems to be in direct contradiction to the claims of Cruickshank and others who attribute most of the acid present in the vagina to the activity of this organism. The data presented above show very little, if any, correlation between the degree of acidity of the secretions and the presence or absence of the aciduric vaginal bacillus, in spite of the fact that bacteriologic examinations of the vaginal secretions of individuals in different age groups seem to show a definite relationship between the frequency of occurrence of this organism and the state of activity of the ovaries which is directly related to the H-ion concentration of the vaginal secretions.

On the basis of the evidence obtained, the production of acid in the vagina seems to depend mainly on the state of activity of the ovary. The ovarian function determines the amount of glycogen present in the vaginal mucosa. This glycogen is probably broken down directly to acid by enzymatic action, as shown by Kienlin's finding of acid secretions in young infants in whom the vaginal tract is sterile; or it may be broken down to glucose by means of enzymes, and this carbohydrate then attacked by the bacteria present in the vagina. Such a theory for the formation of acid does not require the presence of the Döderlein organism, since most of the other bacteria present normally, such as staphylococci, diphtheroids, etc., may attack glucose, with acid formation. The activity of these organisms at low pH levels may be explained by the observation that staphylococci, streptococci, and diphtheroids are frequently found to be viable in the vagina at pH levels below those which limit their growth in the test tube.

Since it has been shown that large amounts of acid can be present in the vaginal secretions without the intervention of the Döderlein bacillus, the use of this organism as an indicator of the state of acidity and health of the vaginal tract seems unwarranted. The application of this organism in a suitable carbohydrate menstruum as a therapeutic agent in the treatment of various types of vaginal infections also seems questionable since large amounts of acid can be produced by the administration of the estrogenic hormone without resorting to the difficult manipulations involved in the preparation of cultures for insertion into the vagina.

CONCLUSIONS

1. The administration of estrogenic substance to individuals in the postclimacterium increases the H-ion concentration of the vaginal secretions.

2. There seems to be no definite correlation between the degree of acidity of the vaginal secretions and the presence or absence of the Döderlein bacillus. A corollary to this is that there seems to be little, if any, relationship between the amount of glycogen present in the vaginal mucosa and the presence or absence of the Döderlein organism.

3. The mechanism for the production of acidity in the vagina may be a dual one, enzymatic and bacterial, the organisms involved being any of the members of the normal bacterial flora which can attack glucose, with the production of acid.

4. The use of the Döderlein bacillus as an indicator of vaginal acidity and health or as a therapeutic measure in the treatment of vaginal diseases by virtue of its acid-producing powers seems questionable.

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BRENNER TUMORS OF THE OVARY

A Clinical and Pathologic Study of Ten New Cases With a Brief Review of the Literature

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HISTORICAL

In 1908 Brenner described three solid ovarian neoplasms occurring among elderly women. Grossly his specimens resembled fibromas but, microscopically, he found scattered islands of squamous epithelial-like cells in a dense stroma of connective tissue. He called the tumor "oophoroma folliculare" but it has since come to be known by the name of this early investigator.

Following this original contribution isolated reports of cases were added. In 1931 Robert Meyer was able to bring to 23 the number of reported examples, a number which had grown to 45 when Bland and Goldstein reported their case in 1935. The literature now contains approximately 70 examples of this newcomer in gynecology.

HISTOGENESIS AND PATHOLOGY

Three hypotheses have been advanced in an effort to explain the origin of these tumors. Meyer, who found in the serosa of Fallopian tubes tiny nests of "Brenner cells" favored the hypothesis of Müllerian metaplasia. Schiller postulated a dislocation of epithelium from the primary urogenital connection. The third hypothesis, namely, that these tumors arise through a one-sided development in a teratoma is based on their frequent association with pseudomucinous cystadenomas.

Brenner tumor is almost always unilateral. Grossly it resembles a fibroma, being whitish in color, and the solid variety is dense and hard. In another group the tumor appears as a solid nodule arising in the wall of a cyst.

Microscopically, the picture is uniform and consists of islands of squamous-like epithelial cells in a dense stroma of fibrous tissue. The peripheral rows of these cells are frequently arranged in palisades. Some of the islands are cystic with an inner lining of columnar mucous-producing cells. Mitotic figures are not observed.

The tumor is to be distinguished from granulosa cell neoplasm and from metastatic squamous-cell epithelioma. This distinction is simply made with the Galantha stain for mucus.

CLINICAL FEATURES

The clinical features of Brenner tumor are those of a slowly growing pelvic neoplasm with none of the usual features of clinical malignancy. Sixty per cent of the neoplasms occur after the menopause.

MATERIAL FOR STUDY

In a study of solid ovarian neoplasms removed surgically at the Mayo Clinic from 1905 to 1937, 10 examples of Brenner tumor were encountered. An analytical study of the clinical histories and pathologic data is presented.

REPORT OF CASES

CASE 1.—A white multipara, aged 46 years, presented herself for examination Sept. 25, 1936, because of a tender lump in the left side of the abdomen. Her family and personal histories were essentially negative. Menses always had been regular until one year prior to admission when, following five months of scanty flow, the periods ceased. Concomitant menopausal "hot flushes" had been noted. Nine months prior to registration she had noticed a firm, tender mass in the lower part of the abdomen. This, together with intermittent vaginal discharge, had caused her to consult a physician who found an ovarian tumor.

Examination revealed a large, firm tumor in the left side of the pelvis and abdomen. There was also marked cystocele and rectocele with an infected cervix. At operation, on Sept. 26, 1936, perineorrhaphy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy were performed with removal of a solid ovarian neoplasm. The postoperative course was uneventful, and the patient was discharged from the hospital on the seventeenth postoperative day.

On pathologic examination, the right ovary was atrophic. Nothing remarkable was noted concerning the uterus except for a cystic condition of the cervix. The left ovary, containing a large corpus luteum, was seen at the lower pole of a solid,

fibrous tumor. The tumor measured 10 by 10 by 8 cm. The smooth surface was lobulated and contained a network of large veins. On section, this mass imparted a gritty sensation, the cut surface being hard and fibrous, not unlike fibroma. No cysts were seen.

Microscopically, the tumor was typical of the Brenner type. Scattered here and there in a dense fibrous stroma containing calcium, were islands of pale-staining epithelioid cells with distinct outlines. These islands were surrounded by a rim of darker staining, condensed stroma. The peripheral layers of cells occasionally were arranged in palisades. Many of the islands had cystic centers and, in some of these spaces, pink staining masses containing epithelial debris were seen. Lining these cysts, the cells of the tumor were arranged in a definite layer suggestive of secreting epithelium. Under high magnification, islands were seen to be composed of large, pale-staining cells with sharp outlines and vacuolization of the cytoplasm. The nuclei were small and the nucleoli relatively pinpoint in size. The cells in the cystic spaces appeared to be desquamated from the lining layer. Transition from normal ovarian elements could not be traced. The corpus luteum was seen to be old and organized and there was a definite capsule between it and the substance of the tumor. Follicles could not be found in either ovary. Stains for fat were negative, but the Galantha mucin stain demonstrated the presence of mucus in some of the cystic cavities.

The interesting feature, in this case, is the presence of corpus luteum in association with the tumor which shows that ovarian function to this extent was not affected. This finding has not been observed in cases of granulosa cell tumor which produces temporary sterility, and points to a different origin of the two types of neoplasm. The presence of amenorrhea could be well explained on the basis of the climacterium, a feature indicated by the associated menopausal symptoms. Leucorrhea and the occasional spotting observed probably could be explained on the basis of cervicitis, a feature which led the surgeon to perform hysterectomy rather than local resection of the tumor. The presence of calcium in the substance of the tumor represents an additional feature of interest (Figs. 1, 2, and 3).

CASE 2.—A white woman, aged 70 years, sought medical advice because of prolapse of the uterus of approximately ten years' duration. Her family and personal histories were essentially negative. She was the mother of five children. The climacterium occurred at the age of 51 years and was without incident.

Her present symptoms took the form of a bearing-down sensation in the pelvis which had been progressive in severity over the period of three months prior to her registration and she had noted, in addition, a slight mucoid vaginal discharge, at one time blood tinged.

Examination was essentially negative except for the presence of uterine prolapse with cystocele and rectocele and, on pelvic examination, the additional finding of a hard, movable tumor of the right adnexal region. At operation on April 17, 1936, anterior colporrhaphy and perineorrhaphy, abdominal hysterectomy, and right salpingo-oophorectomy were performed for prolapse and for a fibroid tumor of the right ovary. The postoperative course was uneventful and the patient was dismissed on the fifteenth day. She was living one and a half years after operation.

Examination of specimens removed at operation revealed a senile type of uterus with atrophic endometrium and considerable fibrosis of the myometrium. The right tube was the site of a small hydrosalpinx, and it was stretched out over the surface of a hard, white, lobulated tumor 6 cm. in diameter, replacing the right ovary. This tumor was cut with considerable difficulty and was like ordinary fibroma except for being darker in color and coarser in texture. No trace of normal ovary could be found.

Microscopically, the tumor was so similar to that of Case 1 that little additional description is necessary. Again, the picture was one of islands of epithelial-like cells with a dense surrounding investment of connective tissue, frequently with cystic centers. The stroma was coarse and fibrous and gave the impression of benignity and slow growth. Mitotic figures were not observed.

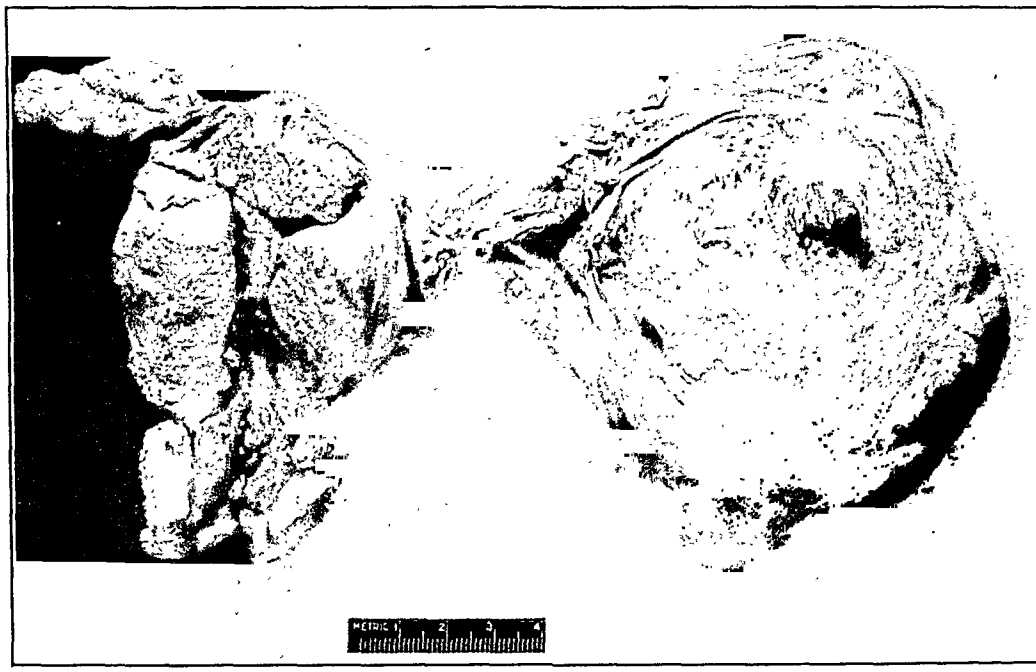


Fig. 1.—(Case 1.) A large solid Brenner tumor of the left ovary removed at operation. Note the corpus luteum at the lower pole of the tumor.



Fig. 2.

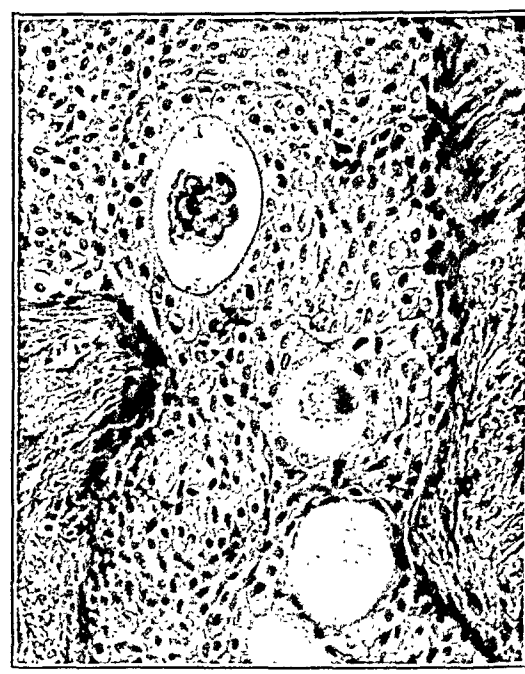


Fig. 3.

Fig. 2.—(Case 1.) Two islands of epithelial cells situated in a dense stroma. (×130.)

Fig. 3.—(Case 1.) An epithelial island containing several cysts filled with debris. Note columnar character of lining cells with transition to squamous type. (×270.)

CASE 3.—A white multipara, aged 53 years, was admitted to the clinic Dec. 5, 1927, with a diagnosis of obstructing carcinoma of the colon for which colostomy had been performed elsewhere six months previously. Her menstrual history had been normal, and her climacterium had occurred two years previously without incident. She was operated upon Dec. 22, 1927. Resection of the sigmoid with anastomosis was performed. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for a solid tumor of the left ovary. The postoperative course was stormy, complicated by bronchopneumonia and terminal parotitis. Death occurred on the fifteenth postoperative day.

The specimen obtained at operation consisted of 10 cm. of sigmoid colon containing annular, ulcerated adenocarcinoma, Grade 2 (on the basis of 1 to 4), 4 by 4 by 2 cm. with several regional nodes involved by metastasis. The uterus, both tubes, and the right ovary were not remarkable. The left ovary was replaced by a solid, firm, grayish tumor measuring 4 by 3 by 2.5 cm., conforming to the general gross description outlined in Cases 1 and 2.

Microscopically, the picture was typical of Brenner tumor. An alveolar structure was entirely lacking, a fact which ruled out the possibility of the tumor being of a metastatic origin from the neoplasm of the sigmoid colon.

CASE 4.—A white multipara, aged 66 years, was admitted to the clinic, Aug. 10, 1933. She gave a history of bleeding for a period of four weeks which occurred twenty years following normal menopause. Examination gave negative results except for slight enlargement of the uterus.

On Aug. 17, 1933, abdominal hysterectomy and bilateral salpingo-oophorectomy were performed because of a report of adenocarcinoma in the endometrial scrapings on examination of a frozen section. A tumor measuring 2 cm. in diameter was found in the right ovary.

Microscopic examination of sections of the nodule, gave evidence of essentially the same picture as found in the specimen of Case 1, typical of Brenner tumor containing foci of calcification. Portions of this as well as portions of the left ovary contained the cortical and medullary tubular rests from which this tumor is supposed to take origin. No stages of transition, however, were obvious. Sections of the endometrium gave evidence of typical adenocarcinoma, Grade 2.

CASE 5.—A married, white woman, aged 61 years, registered at the clinic Dec. 24, 1927, complaining of vaginal "spotting" of six months' duration. Examination disclosed a fibromyomatous uterus with slight bloody discharge from the cervix. A mass in the left adnexal region was palpated. She was operated upon on Dec. 28, 1927, and total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed for uterine fibromyomas and for a left ovarian cyst. This patient was living and well when last heard from in 1935.

Pathologic examination disclosed a uterus with multiple intramural fibromyomas varying in size from 4 cm. to 1 cm. in diameter. At the fundus there was a degenerating adenomatous polyp measuring 4 by 3 by 2 cm. The endometrium was atrophic. Both tubes and the right ovary contained fibrotic changes. The left ovary was replaced by a multilocular pseudomucinous cyst with tiny intracystic papillomatous growths. One of these projections measured 1 cm. in diameter and grossly resembled fibroma. Microscopic sections of this nodule were typical of Brenner tumor.

CASE 6.—A married, white nullipara, aged 34 years, registered at the clinic July 21, 1918, complaining of irregular menses. For eighteen months her "periods" had occurred at intervals of four to seven weeks with profuse flow and considerable dysmenorrhea. Examination revealed multiple uterine fibromyomas and a mass in the left adnexal region. At operation on July 26, 1918, a large solid right ovarian tumor was found with many adhesions between it and neighboring structures. The uterus contained fibromyomas and was removed together with the ovarian tumor, both tubes, and the right ovary.

On pathologic examination, only a small portion of this tumor was preserved. Multiple sections, however, all contained evidence of Brenner tumor of the solid type.

CASE 7.—A married, white nullipara, aged 61 years, registered at the clinic on April 27, 1937, complaining of enlargement of the abdomen of six months' duration. Three years prior to registration, routine physical examination had revealed the presence of a pelvic tumor.

Examination confirmed the previous observation of a pelvic tumor now reaching the umbilicus. At operation on April 29, 1937, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for bilateral ovarian cysts. The patient was living and well nine months postoperatively.

Pathologic examination revealed a small, senile type of uterus. Both Fallopian tubes were chronically inflamed. The right ovary contained a simple follicular cyst 3 cm. in diameter. The left ovary was the seat of a multilocular pseudomucinous cyst 18 cm. in diameter with four solid intracystic nodules from 5 to 1 cm. in their greatest diameters. Examination of sections taken through these solid nodules all gave evidence typical of Brenner tumor.

CASE 8.—A single, white nullipara, aged 34 years, registered at the clinic Sept. 21, 1911, complaining of cramping pain of three weeks' duration in the lower abdomen. Menses had been regular.

On examination, a cystic tumor was palpated in the left adnexal region, for which operation was carried out on Sept. 28, 1911. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed for bilateral ovarian tumors and for uterine fibromyomas. This patient was living and well twenty-five years later.

On pathologic examination, the uterus was found to contain multiple fibromyomas. Both Fallopian tubes gave evidence of fibrous thickening. The right ovary was the seat of a typical multilocular, pseudomucinous cystadenoma, measuring 10 by 8 by 7 cm. The left ovary contained within its substance a fibrous nodule 2 cm. in diameter. Examination of microscopic sections of this nodule proved it to be Brenner tumor. Multiple sections through the wall of the right ovarian cyst failed to demonstrate any comparable picture.

CASE 9.—A married, white multipara, aged 59 years, registered at the clinic on Oct. 21, 1929, complaining of postmenopausal bleeding of nine months' duration. Pelvic examination disclosed an indurated, ulcerated cervix, manifestly carcinomatous. At operation on Oct. 29, 1929, a modified Wertheim type of hysterectomy was performed with removal of the adnexa. Postoperatively, a complete course of roentgen therapy was administered. When last heard from in 1935, this patient was living but had an inoperable, recurrent malignancy.

On pathologic examination, the uterine cervix was the site of squamous-cell epithelioma, Grade 3, measuring 4 by 4 by 3 cm. Both Fallopian tubes were mildly and chronically inflamed. The right ovary was atrophic. The left ovary was fibrotic and cystic but disclosed at its hilus an encapsulated fibrous nodule measuring 1 cm. in diameter. Microscopically, this nodule was typical Brenner tumor of the solid type.

CASE 10.—A married, white multipara, aged 65 years, sought medical advice at the clinic on April 7, 1934 for uterine prolapse of many years' duration. Examination revealed a relaxed perineum with uterine prolapse, Grade 3 (on a basis of 1 to 4).

At operation on April 9, 1934, Mayo vaginal hysterectomy with bilateral salpingo-oophorectomy and perineorrhaphy were performed. Convalescence was uneventful and the patient was living three and one-half years later.

On pathologic examination, the uterine cervix was considerably elongated and contained multiple cysts. Both tubes were chronically inflamed. The left ovary was atrophic. The right ovary, at its uterine pole, had a solid grayish tumor nodule, measuring 2 cm. in diameter. Microscopically, this nodule proved to be Brenner tumor of the solid type.

SUMMARY AND CONCLUSIONS

1. Ten cases of Brenner tumor are presented.

2. This type of tumor probably arises from ectopic ovarian hilar or cortical rests having no counterpart in the normal structural elements of the ovary and producing no physiologic alterations.

3. It occurs most often after the menopause.

4. It may occur either as a solid tumor or as a nodular projection in the wall of an ovarian cyst.

5. It grows slowly and nearly always is benign; prognosis is excellent following even local resection.

6. It may become partially calcified.

7. Brenner tumor of the ovary occurs much more frequently than is suspected. Microscopic sections in any series of so-called ovarian fibroma will bring to light many examples of this "new" and interesting neoplasm.

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THE USE OF TESTOSTERONE PROPIONATE IN THE TREATMENT OF DYSMENORRHEA

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IT APPEARS from recent reports that the immediate cause of pain in essential dysmenorrhea results from excessive spasmodic or tetanic contraction of the myometrium.[1-3] While this phenomenon is frequently associated with autonomic and psychogenic factors, it seems that for the most part such excessive contractions result from an endocrine imbalance. For example, it is known that initiation and maintenance of rhythmic uterine contractility is brought about by the follicular hormones, estrogens, which at the same time sensitize the myometrium to pituitrin.[4] The contractility and sensitization thus produced are diminished by the corpus luteum hormone, progesterone.[5] When estrogens are excessive or progesterone insufficient, exaggerated contraction results which the patient experiences as pain.

One of the earlier attempts to alleviate menstrual pain with an endocrine preparation, the luteinizing substance, antuitrin-S,[3] proved to be rather disappointing. The more direct use of progesterone[6, 7] met with more promising success.

Because testosterone, an androgenic product originally obtained from bull testis, but now synthetically produced from cholesterol, was found to be closely related chemically to progesterone[8] and because some of the androgens experimentally led to phenomena in many respects similar to progesterone,[9-12] it appeared advisable to study its effect upon the dysmenorrheic patient.

Twenty-six such patients were studied. The experiences encountered are best illustrated by the following case reports:

CASE 1.—L. S., white, single, twenty-eight years of age, well developed and nourished. Menstruation began at 14 years, recurred every twenty-four to thirty-five days and lasted four or five days. The flow was normal. Severe dysmenorrhea had been present from the onset of her first menstrual period. The pain which appeared with the flow was so severe that bed rest was required for twenty-four to forty-eight hours. Although she was then able to return to work, marked discomfort persisted throughout the period. Nausea, occasional vomiting, insomnia, and feelings of depression and anxiety accompanied the pain during the first one or two days.

Treatment consisted of two injections of testosterone propionate (Perandren-Ciba) in 5 mg. doses administered subcutaneously on the twentieth and twenty-third days of her menstrual cycle. Menses began on the twenty-fifth day and were practically free of all discomfort. She lost no time from work during this period, since she was free from digestive upsets, sleep disturbances, and the usual feelings of depression. During the next cycle the same treatment was repeated on the twenty-third and twenty-fifth days. Menses began on the twenty-sixth day again free from all discomfort.

During the third cycle it was decided to note the effect of the 10 mg. administered as a single dose. This was given on the twenty-fifth day and was followed the next day by menstruation which was accompanied by marked abdominal pain, nausea, and vomiting.

During the following cycle the hormone was again administered as two 5 mg. doses on the twenty-second and twenty-fifth days. Menses began on the twenty-seventh day with moderate discomfort during the first two hours. In the following four cycles the dose was increased to 15 mg., ten of which were administered on the twenty-second day, the remaining 5 mg. being given on the twenty-fifth day. This dosage has been sufficient to render her symptom-free.

CASE 2.—S. F., white, 13 years of age, studied in cooperation with Dr. M. H. Radman. Her complaint was painful menstruation for a duration of one year. Menses began at 10 years of age, recurred every thirty days and lasted six to seven days. For the first two years everything was normal. Following an attack of influenza and mumps at the age of twelve, there was a delay of menses for twelve days. Since then her periods have appeared regularly but have been accompanied by marked pain which confined her to her home for two to three days. Physical and gynecologic examinations revealed no pathologic findings.

Treatment consisted of 15 mg. of testosterone propionate (Perandren-Ciba) as 3 intramuscular injections of 5 mg. each on the day prior to the onset, when pain was first experienced, and on the first and second days of her flow. Complete relief from pain occurred after the second dose.

CASE 3.—E. R., white, 32 years of age, married six years, one pregnancy, one child living and well at five years, complained of painful menstruation and marked premenstrual tension manifested by swelling, tenseness and marked tenderness of the breasts for five days prior to menses and feelings of congestion and dragging pain in the lower abdomen for two to three days before onset of menses. In addition there was progressively increased emotional irritability during the three days preceding menstruation. Menses began at 15 years, recurred every twenty-five to thirty-five days and lasted seven or eight days. The flow was very profuse. Physical and gynecologic examinations were essentially negative, although her basal metabolic rate was lower than normal (minus 25 per cent). Thyroid medication which was sufficient to increase her basal metabolic rate to normal had no effect on the menstrual symptoms.

Testosterone propionate (Perandren-Ciba) was given intramuscularly in 5 mg. doses 3 times weekly for the last three weeks of her cycle. Menses occurred on the twenty-sixth day of that cycle. Although it was more profuse than previously the flow was smoother. Premenstrual tension and pain were completely relieved. Pelvic

congestion, however, was still present. The same therapy was followed for the next two cycles each of which lasted twenty-seven days. There was complete relief of all symptoms. While the duration of flow remained six days, the amount was reduced considerably.

The next six periods, during which time treatment was withheld, recurred at twenty-seven- to twenty-eight-day intervals, lasted six days, and were symptom-free except for a slight feeling of pelvic heaviness which occurred during the twenty-four hours prior to onset.

CASE 4.—D. E., white housewife, aged 31 years; one pregnancy, one child living at six years. Complained of severe menstrual pain which had become progressively worse during the last ten years. Physical and gynecologic examinations were essentially negative. Menses began at 14 years, recurred every twenty-one to twenty-three days and lasted four or five days. During the last ten years menses lasted seven days, with slight dribbling the first two days, full profuse flow for the next two or three days and diminution thereafter. Severe pain was present from the onset of full flow and remained for about forty-eight hours.

She was given 5 mg. of testosterone propionate intramuscularly three times weekly for the week before the next period. Menses occurred on the twenty-fifth day, were free from pain, and lasted five days. For the next three cycles she received 5 mg. of testosterone propionate 3 times weekly (except during menses). Menses occurred on the twenty-fifth day with complete absence of pain and considerable diminution in amount of flow. For the next two cycles, 5 mg. were given twice weekly (except during menses) with equally good results. For the next five months the patient was taken off treatment. Periods occur now at twenty-four- to twenty-six-day intervals, last five days, and are free from pain. However, staining for one day prior to the free flow has reappeared.

CASE 5.—J. L., aged twenty-four years, white, housewife, whose chief complaint was severe menstrual pain. Physical and gynecologic examinations were negative. Menses began at 15 years, recurred every twenty-one to twenty-five days, lasted six days and were accompanied by pain since her first period. The first two days of the period were marked by mere spotting. With the appearance of full flow, which was profuse, there was marked griping pain in the lower abdomen. Bed rest was required for relief.

She was given 5 mg. of testosterone propionate intramuscularly on the fifteenth, twenty-first, and twenty-fourth days of the cycle. Menses appeared on the twenty-eighth day and were free from pain. However, a slight feeling of pelvic congestion remained. The usual staining was also absent. This period lasted four days but was more profuse than usual. In an effort to diminish the amount of flow she was given 4 doses (5 mg. each) on the thirteenth, sixteenth, eighteenth, and twenty-second days of the next cycle. Menses appeared on the twenty-eighth day without pain and there was moderately reduced flow.

Treatment was discontinued because the patient expressed a desire to become pregnant. After two normal menstrual cycles entirely free from discomfort, she was successfully impregnated (Friedman Test).

CASE 6.—E. B., a 26-year-old housewife, who complained of irregular menses, profuse bleeding and marked pain at the time of menses. Physical and gynecologic examinations were negative. Menses began at 14 years, recurred every twenty-nine or thirty days and lasted four days. During the past one and one-half years, menses had been very irregular with profuse bleeding for four to five days (18 to 20 pads daily), which tapered off for one or two days, only to be followed by a copious flow during the next five to six days. Intermenstrual spotting has been present for the past six months. The pain which appeared twenty-four to forty-eight hours before the onset of the flow was accompanied by marked tenseness and tenderness of the breasts and severe frontal headaches. After its onset, the symptomatology remained for two days, was gradually alleviated during the next four or five days and reappeared with full vigor with the recurrence of profuse bleeding.

An endometrial biopsy taken the day before the calculated date of onset disclosed a normal endometrium characteristic of the follicular phase of the cycle. She was given testosterone propionate (Perandren-Ciba) in 5 mg. doses intramuscularly every other day for 4 doses. Menses set in on the ninth day of therapy; i.e., the flow was apparently delayed for eight or nine days.

The flow during this period was profuse for the first two days but only 8 pads were required instead of the usual 18. Pain was slight. Because of returning pain on the seventh day of this period she was given 10 mg. of the hormone intramuscularly. This was followed by a marked increase in flow that evening which completely subsided by the next morning.

Since then, without further treatment, she has remained practically symptom-free, menses recurred at twenty-eight- to thirty-day intervals, lasting four to six days, being normal in amount. An endometrial biopsy taken two months after treatment on the twenty-third day of the cycle disclosed a secretory picture.

CASE 7.—F. G., white, married but separated; had had 2 pregnancies resulting in 2 living children who are normal, 3 and 6 years of age, respectively. Her complaint was severe menstrual pain and profuse bleeding from the onset of her first period. Menses began at 12 years of age, recurred every twenty-eight to thirty-two days and lasted five or six days. During the first day of her period the flow was scant and pain was crampy and slight in nature. During the second and third days the pain became worse until it was so excruciating that she had to retire to bed. In addition, the flow became very profuse, saturating at least 12 pads daily. Breast pain appeared twenty-four hours prior to the onset of the flow and lasted for about forty-eight hours.

On the second day of her menstrual period just as severe pain was developing she was given her first injection of 5 mg. of testosterone propionate intramuscularly. Within two hours her pain had completely subsided and the relief lasted for the remainder of the period. The amount of flow, however, was slightly but definitely increased. During this same cycle, 5 mg. doses were repeated on the twenty-fourth and twenty-eighth days. Menses appeared on the twenty-ninth day, free from pain. The usual premenstrual breast tension was also absent. Bleeding was as profuse as usual. On the twenty-third and twenty-sixth days of the next cycle the same therapy was repeated. Menses began on the twenty-eighth day with but slight backache and cramps for the first two hours after which she remained asymptomatic. The flow was as usual.

During the third cycle, injections (5 mg.) were given on the twenty-first and twenty-fifth days. Menses set in on the thirtieth day with no pain. The amount of flow was diminished, however, being estimated by the patient as being less than half the usual amount (3 or 4 pads daily). No therapy has been given for the last two periods. The patient has menstruated on the twenty-ninth and thirtieth days, respectively, and aside from slight cramps and mild backache for several hours has remained comfortable. Her flow has remained moderate.

CASE 8.—M. G., white, single, 20 years of age, laboratory technician whose complaint was "dysmenorrhea and profuse menstrual bleeding." While the patient was of slender build, physical and gynecologic examinations were otherwise normal. Menses which began at 11 years of age had always been irregular, recurring every twenty-one to thirty-five days. During the past three years they have been recurring at twenty-one- to twenty-five-day intervals, lasting six or eight days.

The flow was always profuse especially during the first four days when 12 to 15 napkins were saturated daily. Her present complaint dates from her first menstrual period. Pain begins twenty-four to forty-eight hours before the discharge makes its appearance and becomes so severe that at the onset of the flow she has to take to bed where she remains for thirty-six to forty-eight hours. Marked nausea, occasional vomiting, cold sweats and dizziness are present at the height of pain. The last three to five days of flow are accompanied by a continuous ache in the lower abdomen. Once in her entire menstrual history she has been free from pain. This occurred about three years ago.

Treatment was begun on the first day of her menstrual flow at which time she was in agony. Ten milligrams of testosterone propionate were administered, 5 mg. intra-

muscularly and 5 mg. subcutaneously. Relief of pain began in two hours and within twenty-four hours was complete. Her flow, however, was markedly increased in amount that evening but by the next day had decreased to such an extent that she required but 6 pads. During the next two days, only 2 or 3 pads were utilized. In order to completely stop bleeding 30 mg. of the hormone were administered in 3 daily 10 mg. doses intramuscularly during the third, fourth, and fifth days, respectively. While the amount of daily bleeding was diminished the period was extended to eleven days with mere spotting during the last four days. Five-milligram subcutaneous doses were administered on the thirteenth, sixteenth, nineteenth, and twenty-first days of this cycle. Menses began on the twenty-first day and were free from all discomfort and pain. The flow was characterized by mere staining for forty-eight hours, was normal during the third day, then tapered off, to cease on the fifth day.

For the past two months she has received 5 mg. subcutaneously on the nineteenth or twentieth day of the cycle. Menses during these two cycles have occurred on the twenty-sixth and twenty-second days, respectively, with normal flow for a period of five days, entirely free from discomfort.

CASE 9.—H. S., white, single, 31 years of age. Her chief complaint was severe menstrual pain accompanied by nausea and marked premenstrual occipital headaches.

General physical examination showed no gross abnormalities but gynecologic study by Dr. M. H. Radman disclosed a palpable right kidney extending down to mid-abdomen. The cervix was small but the uterus was normal in size; although it was retroflexed in midposition, the uterus was freely movable. The adnexa were negative. Menses began at the age of 11, recurred at twenty-one to twenty-five days, lasting six or seven days. Her present illness dates from her first menstrual period. Various sedatives and anterior pituitary-like hormone were administered for several months without relief. Testosterone propionate was then substituted. Ten milligrams were given on the twenty-fourth day and 5 mg. on the twenty-sixth day of her cycle. Menses occurred on the thirty-second day with a mild discomforting pain in the abdomen which lasted about ten hours the first day. The headache appeared in mild form three hours before the flow which lasted but three days. During the next cycle (twenty-four days) no therapy was given and all her symptoms returned. During the next 4 cycles, however, testosterone propionate administered in various dosages and methods has failed to relieve her symptoms.

CASE 10.—L. G., white, single, 36 years of age, complained of very severe pain associated with menstruation which was accompanied by nausea during the first twenty-four hours of flow and marked premenstrual breast pain a day before the onset. Menses began at 14 years; recurred at twenty-eight- to thirty-day intervals and lasted three days. The flow has always been scant.

Physical examination disclosed an obesity of the pituitary type. The basal metabolic rate was found to be minus 18 per cent. In addition, there was a marked anxiety because of her precarious economic situation. Treatment by means of dietary restriction, pituitary preparation (Pituitrin-O and anterior pituitary extract, Squibb) and sufficient thyroid substance which led to loss of weight and an increased metabolic rate (plus 10 per cent) failed to influence the dysmenorrhea. While psychotherapy involving a discussion of her conflicts led to a diminution of her anxiety and feelings of insecurity, dysmenorrhea continued.

A day before her expected period she was given 10 mg. of testosterone propionate (Perandren-Ciba) intramuscularly. Menses appeared the next day with the usual nausea and pain but the breast pain was absent.

On the twentieth day of her second cycle she received 5 mg. but did not appear for a scheduled injection on the twenty-fifth day. Menses occurred on the twenty-eighth and the pain was worse and lasted longer than usual. The flow also was more marked.

During the third cycle she received 10 mg. subcutaneously on the twentieth and twenty-fifth days. Menses occurred on the twenty-sixth day with freedom from pain except for very mild discomfort. The flow was moderate. Since then, over a period

of five cycles, testosterone propionate given in progressively larger doses during the week before menses (and during one month, throughout the cycle) has failed to relieve the symptoms. During all this time, the patient has consistently refused to undergo a gynecologic examination.

Sixteen additional cases not reported in detail showed features which were not strikingly different from those above so far as the method of treatment is concerned. The results in all the twenty-six cases, therefort, are best summarized as follows:

1. Sixteen patients obtained complete relief. Of these, 15 had a functional disorder and 1 had a chronic salpingitis.

2. Four patients were partially relieved. Of these, 2 had infantile uteri and 2 had retroverted uteri.

3. Four cases failed to respond to the therapy. Of these, 2 were functional, 1 had an infantile uterus, and 1 had a chronic salpingitis.

4. Two patients experienced an aggravation of symptoms. Of these, 1 was functional (?), and 1 had an infantile uterus. One of the patients (L. G.) who was made worse during one of her periods refused to submit to gynecologic examination and has been classed as functional (?).

DISCUSSION

From the foregoing it will be noted that the greatest relief was obtained in patients with "essential" dysmenorrhea. Most observers now believe that hormonal imbalance is the major etiologic factor in these cases. The treatment of this disorder with proper endocrine preparations is, therefore, quite logical.

The use of testosterone propionate in this condition, as explained previously, was based on its progesterone-like action. It is well established that functional dysmenorrhea is frequently associated with high estrogen concentration in blood and urine.[13] This is particularly true just prior to menstruation when, in addition, there is a rise of pituitary gonadotropic substance.[14]

Because testosterone propionate depresses pituitary gonadotropic secretion[15] and inhibits ovulation[16] it leads to the suppression of estrogen formation. In addition, by favoring luteinization and maintaining the corpus luteum,[17] it increases the progesterone-like effect. This leads to myometrial relaxation, myometrial growth through its trophic effect, and progestational response in the endometrium.

The most striking effect clinically, however, is the relief of menstrual pain. That this results from uterine relaxation is indicated by preliminary studies on "afterpains" which were also relieved by this hormone.

The relief of premenstrual tension and profuse bleeding is also explainable on the progesterone-like effect of the substance used.

CONCLUSION

Testosterone propionate has been found to relieve most cases of essential dysmenorrhea. It has not been as helpful in organic or anatomically determined dysmenorrhea. This substance will frequently relieve

and in some cases cure the varied aspects of premenstrual tension. It has been found to be a valuable asset in functional uterine bleeding.

The authors appreciate the cooperation of Ciba Pharmaceutical Products Inc., for partially defraying the expenses involved in this study.

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BILATERAL INTRALIGAMENTOUS LIPOMAS OF THE BROAD LIGAMENT

REPORT OF TWO CASES

G. LEE STAGG, M.D., AND WARREN C. HUNTER, M.D., PORTLAND, ORE.

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USING the literature alone as an index, intraligamentous lipoma is a rare tumor, only 14 examples having been recorded to date and of these two were not regarded as true neoplasms. On the other hand the fact that Watkins[1] has observed several broad ligament lipomas in his operative gynecologic cases during the past several years and has not reported them, lends support to the well known fact that some of the apparent rarities in human pathology are more common than is generally supposed, solely because they are not put on record.

The condition was first mentioned by Pollock[2] in 1852. He encountered one instance of simple lipoma in the substance of the broad ligament in a series of 538 necropsies. In 1919 Lockyer[3] discovered another at an operation for dermoid cyst of an ovary. The lipoma, typical in form, lay in the broad ligament in contact with the dermoid, entirely free from the cyst or its contents although lipoid matter did extend along the external wall of the cyst. Lockyer reviewed the literature and found 9 other cases, 7 of which he regarded as true lipomas. Two were rejected because of their association with dermoids. In one the cyst had ruptured, allowing dissection of the fatty contents between the layers of the broad ligament; the other showed an infiltration of fatty material into the broad ligament and about the dermoid. In 1926 Rawls[4] published his account of an operation on a negress for multiple fibromyoma and ovarian cyst in whom the supposed cyst proved to be a large lipoma in the left broad ligament. In a survey of the literature Rawls mentions Lockyer's case and adds those of Pollock and Klein which appeared in 1909. A careful check of the literature from 1926 to March, 1938, has disclosed only one additional instance, that of Kanter,[5] in 1935. The clinical history in this case justified the diagnosis of incomplete abortion. Vaginal examination disclosed a very small uterus which was displaced laterally; on the left side was a rather soft tumor

that reached the crest of the ilium. The preoperative diagnosis was hydrosalpinx. The uterus and tubes proved to be normal, but one broad ligament contained a more or less lobulated lipoma about 20 cm. in diameter which shelled out easily from the folds of the ligament excepting at the lower pole where it was intimately associated with the deep pelvic and femoral vessels from which the blood supply was derived.

Lockyer's summarization reveals only one example of bilateral lipoma of the broad ligaments, that of Emrys-Roberts, who described a small tumor of this type in each ligament in conjunction with an ovarian fibroma and multiple uterine fibroids.

According to Rawls the lipomas hitherto observed have varied from diameters of a few centimeters to "very large size." Middelschulte[6] removed one weighing thirty-three pounds and measuring 88 by 90 cm. The age of the patients has ranged from 31 to 64 years. In three of the reported cases and in one of ours, intraligamentous lipoma constituted the sole lesion; associated pathology was present in five, while the remainder are silent on this point. In most instances the symptoms have led to the preoperative diagnosis of ovarian cyst.

The rarity of broad ligament lipomas is believed to be due to the normal lack of fat in this location. While several possible etiologic factors have been proposed none are at all convincing. Metaplasia from connective tissue is a possible factor.

CASE REPORTS

1. Mrs. R. W. W.,* aged 55 years, complained chiefly of pain in both lower quadrants; this symptom had been present for approximately a year, was intermittent in type and of increasing severity, lasting two to three days. For the past few months she had been conscious of a swelling in the left side of the abdomen. In addition there was some frequency of urination and nocturia (2-3 times). Over a five-year period, but subsiding two years ago, vaginal bleeding occurred every three months. Menstruation began at the age of twelve, was of twenty-eight day cycles, lasted two to three days and was never excessive. Four pregnancies resulted in three living children and one miscarriage.

Pertinent Physical Findings: The abdomen was too obese for satisfactory examination by palpation. There was a slight tenderness immediately above the left inguinal region. On bimanual palpation the uterus seemed to be normal in size and position; a soft, somewhat boggy mass was felt in the left adnexa and a smaller one of similar consistency was made out on the right side. The preoperative diagnosis was left intraligamentous parovarian cyst. The laboratory reports on blood, urine, and serology were essentially normal and are therefore omitted in order to conserve space.

On opening the abdomen the enlarged and widened broad ligaments of the uterus were seen to encase quite large masses of yellow tissue, the larger swelling being on the left side. The anterior reflection of one broad ligament and the posterior aspect of the other were incised parallel to the round ligaments and oviducts. The fatty tumors were then easily removed by blunt dissection. There proved to be four separate and distinct masses, two on either side. The patient made an uneventful recovery.

Pathologic Description: Four quite discrete tumors having a combined weight of 270 gm. were present. Externally two appeared quite smooth and regular in contour, while the others presented somewhat serrated and lobulated outer surfaces. The dimensions of the several specimens were 6.5 by 4 by 3 cm., 8 by 6 by 3 cm., 11 by 10 by 3 cm., and 9 by 6 by 4 cm. Multiple sections through each growth revealed all to consist very largely of quite pale yellow adipose tissue with only a slight admixture of fine fibrous trabeculae. Quite a number of small blood vessels could be made out.

Microsections from each tumor disclosed mostly fat cells of adult type, variable in size and shape and possessing cell membranes that quite often seemed to be thicker than is the case for normal adipose tissue. None were immature and lipoblasts proved to be altogether lacking, thus excluding liposarcoma.

Pathologic Diagnosis: Bilateral intraligamentous lipomas.

*We are indebted to Drs. W. B. Holden and L. T. Nelson for permission to report this case.

2. Mrs. C. A. DeW., 70 years of age, sought attention for profuse vaginal bleeding of only three days' duration, accompanied by slight lower abdominal discomfort. Except for the common signs of senility and poor body nourishment, the physical examination was negative. A diagnostic curettage yielded friable material which in immediate frozen sections was interpreted as an anaplastic adenocarcinoma of the corpus uteri. Upon opening the peritoneal cavity Drs. Holden and Rippey observed no evidence of extension of the neoplasm to the surface of the uterus or beyond it and accordingly performed a panhysterectomy.

Pathologic Description: The entire uterus, either ovary and both tubes had an aggregate weight of 100 gm. Obliterating the left cornu and spreading out over the anterosuperior aspect of the cavum uteri was a crateriform mass, 2.5 cm. in maximum diameter, which had destroyed the myometrium to within 1 cm. of the external surface; the endometrium elsewhere was thin, obviously atrophied and noncarcinomatous. The ovaries were small and atrophic; the oviducts were unchanged.

The mesosalpinx division of the left broad ligament was present posteriorly and in part anteriorly as well but all of the remainder of the ligament had been divided at the uterine end. Viewed anteriorly one could see on this side, adjoining the uterus and between the tube and ovary, a mass of ordinary appearing yellow fat, measuring 3 cm. in length, 2 cm. in breadth and 1 cm. in thickness anteroposteriorly.

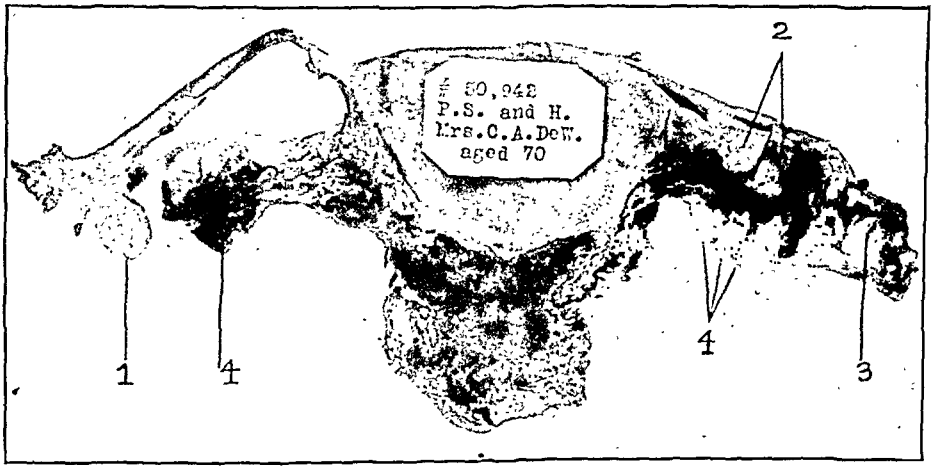


Fig. 1.—Anterior view of uterus and adnexa from Case 2. *1*, Lipoma near fimbria of right tube; *2* and *3*, two of the four lipomas in the left mesosalpinx; *4*, ovaries.

Continuous with this, still lying between the folds of the mesosalpinx, were two additional fatty lobules, covering an area 2.2 by 1.5 by 0.5 cm. Between the epoöphoron and the tubal ampulla, against which it abutted, was another discretely outlined body of fat 1.5 by 1.3 by 0.5 cm. whose lateral border came within 1 cm. of the tubal fimbria. From the opposite side of the mesosalpinx only the two more laterally placed masses could be discerned beneath the peritoneal covering. None of the fatty masses compressed the tube or extended into the hilum of the ovary.

On the right side the only portion of broad ligament present was a triangular segment, 2.5 cm. in breadth, situated inferior to the ovarian ligament posteriorly. Attached to the inferior and denuded aspect of the right tube, 5 mm. mesial to the fimbria and obviously having been interposed between the layers of the missing mesosalpinx was an ovoid yellow blob of fat, measuring 1.5 by 1.5 by 0.6 cm. and containing a goodly number of small and engorged blood vessels running parallel with one another and at a right angle with the tube. Near the tubal attachment the otherwise smooth and regular surface was interrupted by a small hornlike tab of fat. Just inferior to the hilum of the right ovary, but not extending into it, was another accumulation of fat, crescentic in outline and measuring 1.5 by 0.5 by 0.5 cm.

Microscopic sections from the various fatty masses displayed an abundance of fully differentiated fat cells, varying from normal only in being somewhat larger in diameter and apparently thicker walled.

Pathologic Diagnosis: Adenocarcinoma of corpus uteri (Grade III); senile atrophy of uterus and adnexa; bilateral small intraligamentous lipomas, limited to mesosalpinx portion of these structures.

COMMENT

Among the uncommon tumors of the female generative organs one of the least frequent appears to be intraligamentous lipoma. A plausible explanation for this is the normal absence of adipose tissue between the folds of the broad ligaments. False lipomatous growths have been known to occur in conjunction with dermoid cysts of the ovaries. It is also possible for a retroperitoneal lipoma originating in the vicinity of the ligaments to present itself between the leaves of the structure and thus appear to have originated here. Of the twelve acceptable examples hitherto recorded, only one in addition to the two herein described has proved to be bilateral.

When sufficiently bulky, growths of this type are fully capable of manifesting themselves clinically as exemplified in Case 1. This tumor and some of those already in the literature simulated an ovarian or parovarian cyst.

In the second instance, the small size of the lipomas both individually and collectively readily explains their clinical silence. This case is included only on account of the rarity of broad ligament lipomas, the apparently unique localization in the mesosalpinx and the bilateral distribution of the masses. We have been unable to find descriptions of lipomas limited to the mesosalpinx among the previously recorded examples. Sampoerno's[7] case differs from ours in that the lipoma lay beneath the tubal serosa, opposite the mesosalpinx, where it produced marked compression of the lumen. It might be argued that the fatty masses we have described are not lipomas. However, the occurrence in a situation normally devoid of any appreciable amount of adipose tissue, the formation of discrete masses and the presence of such nodules in a woman with little body fat anywhere, make it reasonable to assume that the accumulations are really lipomas.

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SUPERFETATION IN UTERUS DIDELPHYS

Irvin T. Soifer, M.D., Brooklyn, N. Y.

Mrs. B., 22 years of age, a young, robust, well-formed female, weighing 120 pounds and 5 feet 4 inches tall, first seen March 2, 1937.

First menstrual period at 10½ years of age, always irregular, considerable bleeding, 6 to 7 days. Last period on Nov. 1, 1936. Fundus about one finger about the symphysis. Vaginal examination disclosed two distinct and separate introiti divided by a thick septum extending from immediately beneath the urethral orifice to the frenulum labiorum and reaching to the pouch of Douglas and apparently fusing with it, thus forming two complete and separate compartments, each one presenting a distinct and normal cervix.

Bimanual palpation did not disclose any other unusual findings. Neither the patient nor the husband were aware of any abnormality. She never complained of any discomfort due to her pregnancy, except for an occasional slight pyrosis. At the end of the seventh month an x-ray plate was taken. The skeleton of an apparently normal fetus was found on the right side, vertex presentation, measuring twelve inches from vertex to coccyx. There was nothing indicated on the left side to the presence of another pregnancy.

On July 12, 1937, I was called to see the patient at her home. At that time she complained of slight pain in the back and some "spotting." Rectal examination showed no dilatation of the cervix. Patient was given half a grain of codeine twice daily and ordered to stay in bed.

On July 13, at 9 P.M. the patient complained of severe bleeding and of passing "large pieces of something." Upon examination it was found that there was a moderate amount of bleeding and that large pieces of placental tissue were protruding from the vagina, besides a considerable amount of placental tissue passed before my arrival. I could not locate the fetal heart. The patient was taken to the hospital and a vaginal examination done. The cervix on the left side was dilated about 1½ to 2 fingerbreadths. Pieces of placenta and many large blood clots were found in the vagina. The cervix on the right side was completely closed. The patient insisted that she could feel the baby on several occasions during the examination, but no heart sounds were audible. At this point an immediate cesarean section was decided upon with the idea in mind that the fetus was still viable.



Fig. 1.—Lipiodol injection three months after operation.

A lower midabdominal incision was made. A gravid uterus containing an eight to nine months' pregnancy with the placenta attached low on the anterior wall and partly obliterating the internal os was found. The placenta was perforated and an almost full-term fetus extracted.

To the left of the emptied uterus another, about the size of a two months' pregnancy, with normal tube and ovary, was found lying in the left half of the pelvic cavity. A pronounced plica umbilicalis media extended downward from the umbilicus and acted as a curtain between the two uteri.

About twenty hours after the operation, the vulval pad was examined. A fetus measuring 1¾ inches (4.4 cm.) in length from crown to coccyx was found. It seemed that the embryo had been dead not over seventy-two hours, as it was very well preserved, except for the lack of several strips of skin over various parts of the body. The patient's convalescence in the hospital was uneventful and she left on the twelfth day after the operation with a 7-pound living male child, completely recovered.

The foregoing evidently was a case of true superfetation.

451 KINGSTON AVENUE

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

MATERNAL AND CHILD HEALTH SERVICES

THE extent and distribution of Federal grants under the Social Security Act for the fiscal year ending June 30, 1938, are presented in a report made by Dr. Edwin F. Daily, Director of the Division of Maternal and Child Health of the Children's Bureau. This is based on reports received from State health agencies, which are preliminary and incomplete and represent primarily activities of various health departments but include services provided by other public and private agencies. The collected information discloses, however, the extent of governmental activities in this field.

Medical Services.—

Conferences for maternity service, total patients' visits			281,210
Ante-partum service		263,165	
Post-partum medical examination		18,045	
Conferences for child hygiene service, total patients' visits			939,031
Infants		481,358	
Preschool children		457,673	
Health examinations of school children			1,994,342

Public Health Nursing Service.—

Total office and home visits			6,222,723
Maternity service, total office and home visits		1,061,388	
Ante partum	597,043		
Delivery	14,655		
Post partum	449,690		
Child hygiene service, total office and home visits			5,161,335
Infants	1,279,420		
Preschool children	1,072,917		
School children	2,808,998		

Immunizations.—

Diphtheria, number of persons immunized	995,434
Smallpox, number of persons immunized	1,619,190

Dental Inspections.—

Inspection by dentists or dental hygienists, total		1,525,025
Preschool children	127,545	
School children	1,397,480	

Midwife Supervision.—

Midwives under planned instruction, as of June 30, 1938	11,127
Number of midwife meetings	11,294
Attendance at midwife meetings	68,820

AMOUNTS BUDGETED FROM MATCHING AND FEDERAL FUNDS IN STATE MATERNAL AND CHILD HEALTH BUDGETS FOR THE FISCAL YEAR ENDING JUNE 30, 1939

For Professional Personnel and Services, and Postgraduate Education

Grand Total	$6,102,396.55	100%	
Professional Personnel and Services.—			
Total	*5,859,058.41*	96%	
Salaries and travel for 456 state and local staff physicians	1,034,489.76	17%	
Fees to local practicing physicians for conferences, school medical examinations, and home delivery service and consultation	316,014.14	5%	
Salaries and travel for 67 dentists, 52 dental hygienists, and 2 dental health educators on state and local staffs	305,341.56	5%	96%
Fees to local dentists	88,249.04	2%	
Salaries and travel for 43 nutritionists	126,245.15	2%	
Salaries and travel for 34 health educators	101,081.96	2%	
Salaries and travel for 2,822 public health nurses	3,866,382.29	63%	
Fees to local practicing nurses for home delivery service	21,254.51	*	
Postgraduate Education.—			
Total	*243,338.14*	4%	
Medical	146,836.14	3%	
Nursing	83,951.99	1%	
Dental	8,765.00	*	4%
Health education	3,115.01	*	
Nutrition	670.00	*	

*Less than 1 per cent.

Society Transactions

AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS AND ABDOMINAL SURGEONS

FIFTY-FIRST ANNUAL MEETING

White Sulphur Springs, W. Va., September 22, 23, and 24, 1938

The following papers were presented:

Presidential Address—Obstetrics and Gynecology as a United Specialty. Dr. Paul Titus, Pittsburgh, Pa. (For original article, see page 545.)

The Etiology of Occiput Presentations. Dr. L. A. Calkins, Kansas City, Mo. (For original article, see page 618.)

Sterility Studies. Dr. Otto S. Krebs, St. Louis, Mo.

Recent Developments in Diagnosis and Treatment of Hydatidiform Mole and Chorioepithelioma. Dr. Albert Mathieu, Portland, Ore. (For original article, see page 654.)

Clinical Syndromes Referable to Failure of Ovulation. Dr. Emil Novak, Baltimore, Md. (For original article, see page 605.)

Inversion of the Uterus With Repeated Hemorrhages and Replacement by the Use of the Aveling Repositor. Dr. J. K. Quigley, Rochester, N. Y. (For original article, see page 696.)

The Biologic Significance of the Fetal Membranes. (Joseph Price Oration.) Dr. Charles Burger, Budapest, Hungary. (For original article, see page 572.)

Behavior of the Basal Metabolism in the Course of Developing Toxemia of Pregnancy: Correlation With Cholesterol, Placental Infarcts and Retinal Examination. Drs. D. Colvin and R. A. Bartholomew, Atlanta, Ga. (by invitation). (For original article, see page 584.)

Management of Breech Delivery in Primiparas. Dr. Thomas R. Goethals, Boston, Mass. (by invitation). (For original article, see page 663.)

Maternal and Fetal Expectations With Multiple Pregnancy. Dr. John C. Hirst, Philadelphia, Pa. (by invitation). (For original article, see page 634.)

The Relation of Ureteral Pain to Menstruation. Dr. Nathan P. Sears, Syracuse, N. Y. (For original article, see page 685.)

Puerperal Sepsis. Dr. Carl H. Davis, Wilmington, Del.

The Increased Incidence of Fetal Abnormalities in Cases of Placenta Previa. Dr. J. P. Greenhill, Chicago, Ill. (For original article, see page 624.)

Benign Tumors of the Cervical Stump Following Supravaginal Hysterectomy. Dr. Mortimer N. Hyams, New York, N. Y. (For original article, see page 690.)

The Pitfalls of Podalic Version and Extraction. Dr. Milton G. Potter, Buffalo, N. Y. (For original article, see page 675.)

Prevention and Treatment of Postoperative Thrombophlebitis. Drs. N. W. Barker and V. S. Counseller, Rochester, Minn. (For original article, see page 644.)

Studies on the Endometrium in Association With the Normal Menstrual Cycle, With Ovarian Dysfunctions and Cancer of the Uterus. Dr. Wallace E. Herrell, Rochester, Minn. (For original article, see page 559.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Extrauterine Pregnancy

Pütz, T.: Extrauterine Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. 104: 57, 1936.

The author studied a series of 300 cases of ectopic pregnancy. He believes the chief cause is to be found in inflammatory changes of the genitalia. Helpful procedures in making a diagnosis are as follows: (1) The white blood count and the sedimentation test, (2) bimanual examination under evipal, (3) puncture of the cul-de-sac of Douglas, (4) exploratory curettement of the uterus, (5) the Aschheim-Zondek pregnancy test, and (6) exploratory laparotomy.

In the author's clinic, every patient with an ectopic gestation is operated upon as soon as the diagnosis is made. The operation is usually limited to removal of the involved tube. The death rate in this series was 2 per cent.

J. P. GREENHILL

Nixon, W. C. W.: Aids in the Diagnosis and Treatment of Ectopic Gestation, Brit. M. J. 2: 579, 1937.

In the diagnosis of ectopic gestation one must evaluate carefully the history, symptoms, and signs. The history of recurrent attacks of low abdominal pain, accompanied by periodic or continuous uterine bleeding, is very significant. Pulsation in one or other fornix is always present and confirms the diagnosis. It is felt best at the junction of the vagina and cervix by gentle palpation. Puncture of the posterior fornix is a useful aid in diagnosis, if doubt exists, in the acute tubal rupture type.

Treatment is operative in all cases of hematocele, no matter how small it is and irrespective of how ill or well the patient appears to be. Drainage should be avoided. The author favors autotransfusion in the acute cases, where there is free intraperitoneal bleeding and absence of infection. The abdominal route should be employed in all cases in the absence of infection. Where, however, an hematocele has become infected and a pelvic abscess is present, drainage through the posterior vaginal fornix is the method of choice. Seven cases of diverse type are reported.

F. L. ADAIR AND S. A. PEARL

Hope, Robert B.: The Differential Diagnosis of Ectopic Gestation by Peritoneoscopy, Surg. Gynec. Obst. 64: 229, 1937.

The diagnosis of ectopic gestation is not always simple. In the differential diagnosis, peritoneoscopy is a valuable adjunct. It is a safe procedure and in cases of actual intrauterine pregnancy, an abortion is far less likely to occur after it than after exploratory laparotomy.

In questionable cases peritoneoscopy can be used to determine by direct eye-control whether surgery or expectant treatment is indicated. Ten case histories are presented to show the procedure in this field.

WILLIAM C. HENSKE.

Siddall, R. S., and Jarvis, Charles: Uterine Curettage as an Aid in the Diagnosis of Ectopic Pregnancy, Surg. Gynec. Obst. 65: 820, 1937.

In view of the frequent difficulties met with in the recognition of ectopic pregnancy, a study was made of uterine curettage as a diagnostic aid. The pro-

cedure is apparently not unduly dangerous, and the finding of intact decidua without chorionic villi is strong presumptive evidence of extrauterine pregnancy. In 38 cases of proved ectopic pregnancy with available specimens of endometrium, intact decidua alone was present in all cases with abnormal bleeding of ten days or less and in a considerable proportion of those with more prolonged bleeding. The absence of decidual reaction is not reliable evidence against ectopic pregnancy. However, if chorionic villi are also absent, the findings may be of value in ruling out uterine abortion as a cause of the bleeding. Three of four somewhat comparable series found in the literature confirmed the results in large part. Two illustrative case reports are given.

WILLIAM C. HENSKE

Bortini, Ennio: Confirmation of the Various Forms of Ectopic Pregnancy by Hysterosalpingography, Ann. di ostet. e ginec. 16: 1247, 1937.

The author points out the characteristic x-ray signs of the various forms of ectopic pregnancy. This method offers the assurance of a correct diagnosis not only of ectopic pregnancy but also the differentiation of its various forms and their complications.

He emphasizes the necessity of numerous x-ray plates and a long fluoroscopic examination.

He further recommends that the procedure be limited to the doubtful cases, to maintain an aseptic techniue and to be prepared for immediate intervention.

AUGUST F. DARO

Massé and Laporte: High Pain and Leucocytosis in Ruptured Ectopic Pregnancy, Bull. Soc. d'obst. et de gynéc. 26: 282, 1937.

The usual signs of ruptured tubal pregnancy are not always sufficient to permit a diagnosis of this condition. Certain signs, however, may be of help. Among these are pain high up and hyperleucocytosis. This pain appears a few hours after rupture but not when the rupture actually occurs and is due to peritoneal inundation of blood. It usually continues for twenty-four to forty-eight hours after operation but may persist for many days. It is always high up in the thoracic region, always unilateral, and always on the right side. However, this sign is not pathognomonic of ruptured ectopic pregnancy, because it may exist in many other conditions, medical as well as surgical. It is not always present but when it occurs it has a prognostic value because it indicates severe hemorrhage.

An increase in the number of white blood cells is also of prognostic importance because it denotes acute hemorrhage. It occurs early and is an indication for immediate operation. This sign likewise is not pathognomonic of a ruptured tubal pregnancy.

J. P. GREENHILL

Ehrhardt and Kramann: Clinical and Hormonal Errors in Diagnosing Ectopic Pregnancies Because of Corpus Luteum Cysts, Zentralbl. f. Gynäk. 60: 2642, 1936.

The writers report the case of a woman who, after missing a menstrual period, developed sudden pain in the lower abdomen and collapsed. Examination revealed an enlarged uterus and a cystic mass to the right of the uterus. An Aschheim-Zondek test was positive. A diagnosis of ectopic pregnancy was made and a laparotomy performed. However, no pregnancy was found but a cyst of the right ovary. It was removed and proved to be a corpus luteum cyst. Another Aschheim-Zondek test was made the day after operation, and again it was positive. Hence, in this case the hormone pregnancy test was fallacious.

A similar case was recently reported by Kaiser. The Aschheim-Zondek test as a specific test of pregnancy has limitations. Cases of persistent corpus luteum may give a positive reaction. On the other hand, ectopic pregnancy may be present also when the test is negative.

J. P. GREENHILL

Banister, J. Bright: Simultaneous Intra- and Extra-Uterine Pregnancy, Proc. Royal Soc. Medic. 30: 562, 1937.

Patient was a primigravida, in fourth month, without any complaint, presenting herself for antenatal care. A tumor on the left of pregnant uterus was diagnosed as ovarian cyst complicating pregnancy. At laparotomy the ovoid tumor on the left was found to be the size of a twelve weeks pregnant uterus and to represent an ectopic pregnancy in an accessory horn. Mass was excised but the intrauterine pregnancy continued undisturbed to term with delivery of a live infant.

HUGO EHRENFEST

McIlrath, Muriel B.: Bilateral Tubal Pregnancy, Brit. M. J. 1: 1065, 1937.

This is a case of bilateral tubal pregnancy in a gravida ii with a definite history of several attacks of salpingitis. The latter condition may be an etiologic factor in the incidence of tubal pregnancy. The operative findings are described, and methods of treatment discussed. The author favors double salpingectomy with conservation of the ovaries or portions of the ovaries, and the uterus.

F. L. ADAIR AND S. A. PEARL

Martz, Harry: Repeated Ectopic Pregnancy Simulating Intestinal Obstruction, Am. J. Surg. 40: 483, 1938.

A case of repeated ruptured tubal pregnancy with secondary abdominal implantation which simulated a case of low ileal obstruction is presented. The incidence of repeated ectopic gestations is discussed, and the importance of examination of the opposite tube is emphasized in determining the operative procedures to be carried out at the time of operation. The reasons for the clinical findings in this case are mentioned with the aim of emphasizing the importance of shoulder pain, jaundice, midline colicky pains, together with vomiting, distention and obstipation, in the diagnosis of the obscure case of the less dramatic type of ectopic pregnancy.

J. THORNWELL WITHERSPOON

Bellei, A.: A Case of Cervical Pregnancy, Clin. Ostet. 15: 19, 1937.

A case of primary cervical pregnancy is reported, in which the clinical diagnosis of carcinoma of the cervix complicating pregnancy had been made but corrected by microscopic section. The incidence is rare since only 32 cases of this condition are reported in the literature.

AUGUST F. DARO

te Groen, L. J.: An Interesting Case of Tubal Pregnancy. South African M. J. 11: 236, 1937.

The author describes a case in which ectopic pregnancy recurred repeatedly in a patient whom he had treated nonoperatively on two occasions. The patient had a left ruptured tubal pregnancy verified at operation in 1923. Two years later a similar episode, diagnosed as a right ruptured tubal pregnancy, was treated with rest, ice bag, fomentations, etc. The patient recovered after three weeks' hospital care. In the same year she experienced a similar episode diagnosed as a second ruptured ectopic pregnancy with nonoperative treatment; it took her seven weeks to recover. In 1930 a diagnostic curettage was performed for dysmenorrhea. Two months later this was followed by a normal intrauterine pregnancy. In 1931 she delivered a normal healthy baby per vias naturales. She subsequently had two more normal pregnancies.

On Jan. 30, 1937, she was admitted to the hospital with a right ruptured tubal pregnancy. Operation revealed the hemorrhage occurring from the fimbriated end, and the tube was as thick as a finger. About one inch from the uterus the tube became of normal thickness. The ovary was fibrotic. Both tube and ovary were removed.

F. L. ADAIR AND S. A. PEARL

Reid, Ronald: A Case of Abdominal Pregnancy, Brit. M. J. 1: 1301, 1938.

A description is given of an abdominal pregnancy diagnosed by laparotomy in a previously normal woman, aged 31 years, para ii. The possibility in this case is that it started as an ectopic gestation in a Fallopian tube when at six weeks a tubal abortion occurred. The extravasated embryo retained enough of its old connections to survive and grow. Abdominal pain was the outstanding symptom, as well as signs of internal hemorrhage. Control of hemorrhage from the placental attachments at operation was effected by pressure of hot packs.

The literature and statistics are briefly reviewed.

F. L. ADAIR AND S. A. PEARL

Guzman, Gazitua, and Valeuzuela: Two Cases of Intraligamentous Pregnancy at Term, Bol. Soc. chilena de obst. y ginec. 11: 160, 1937.

The authors' first case was in a gravida iv who came into the hospital complaining of irregular vaginal bleeding and an enlarging abdomen. The admission diagnosis was ovarian cyst. X-ray examination revealed an almost full-term fetus. Abdominal pain was present and an expectant plan of treatment was followed. The pregnancy was considered intrauterine. After an appreciable length of time, a laparotomy was done because of the peculiarities present. An extrauterine dead fetus weighing 2,100 gm. and 48 cm. in length was found in an intraligamentous sac. The placental attachment necessitated a bilateral salpingectomy and hysterectomy. A urinary fistula developed due to severance of one ureter.

The second case was diagnosed fibromyoma of uterus because of age of patient (44), and a negative Friedman test. The placenta in this case was easily removed from the broad ligament. A dead fetus weighing 1,750 gm. and 44 cm. long was delivered. Drainage was instituted through the pouch of Douglas. Postoperative convalescence was normal.

MARIO A. CASTALLO

Patrick, A.: Advanced Extra-Uterine Pregnancy, Brit. M. J. 1: 1156, 1937.

The author reports a case of an advanced ectopic pregnancy in the ampullary portion of the Fallopian tube. No history of menstrual irregularities, usually seen in ectopic pregnancy, was obtained. The patient had been sterile for six years prior to this gestation. An emergency operation in the acute illness of this patient revealed the true nature of the pregnancy.

Rupture of ectopic pregnancies usually occurs at the eighth week and very few continue after twelve weeks. This pregnancy advanced to nearly five months.

F. L. ADAIR AND S. A. PEARL

Ormazabal, Olga Moretta: Tubal Pregnancy of 4½ Months, Bol. Soc. chilena de obst. y ginec. 1: 323, 1936.

The author could find no reference in the literature of a similar tubal pregnancy which had advanced so far before rupture occurred. The author claims that in her case the ovisac with placenta was found entirely surrounded by the Fallopian tube wall.

MARIO A. CASTALLO

Vilalta, F. S.: Study of Retention of an Ectopic Pregnancy to Term, Rev. méd. cubana 49: 1, 1938.

A case of full-term ectopic pregnancy is reported by Vilalta. The Friedman test was negative, hence was not helpful. A simple x-ray picture did not reveal the true state of affairs but a uterosalpingogram showed a normal uterine cavity of nonpregnant size, quite distinct from a full-term fetus which presented by the breech. The author operated and removed both the baby and the placenta. No difficulties were encountered. The patient made an excellent recovery.

J. P. GREENHILL

Crichton, E. C.: Full-Time Ectopic Pregnancy, South African M. J. 11: 229, 1937.

Three cases of ectopic pregnancy at or near term are reported. In Case 1 there was no history of vaginal bleeding or abdominal discomfort throughout gestation. An attempted medical induction revealed the absence of uterine contractions following the administration of pituitrin. This may be a useful test in the diagnosis of advanced ectopic pregnancy or other extrauterine tumors.

Case 2 was characterized by abdominal pain throughout pregnancy which was unwisely ignored. At operation a portion of placenta was left behind without drainage and caused no harm. Cases are on record in which the whole placenta was left in the abdomen and subsequent normal pregnancies occurred.

Case 3 is remarkable because the child up to term attained a weight of 9 pounds and, though macerated at operation, showed no serious deformity.

The vast majority of babies which develop outside the uterus are below the average weight and display more or less serious deformities.

F. L. ADAIR AND S. A. PEARL

Lailey, W. W.: An Unusual Case of Extrauterine Pregnancy, Canad. M. A. J. 36: 67, 1937.

The writer reports an ovarian pregnancy in a 35-year-old woman, para iii, gravida v. The patient had vaginal spotting for three months with increasing abdominal discomfort. Vaginal examination revealed the fetal head bulging into the vaginal vault. The cervix was not found until the patient was anesthetized.

On abdominal incision, a uterus the size of a three months' pregnancy was found and a thin-walled sac enclosing the extrauterine fetus.

To control the hemorrhage caused by the placental edge separating, the uterus, right tube, and ovary and as much of the sac wall as could be were resected. Treatment for shock and hemorrhage was given.

The ectopic pregnancy had developed to a state four or five weeks beyond term and survived. The implantation was apparently on the ovary. Mother and baby survived.

H. CLOSE HESSELTINE

Holtz, F.: The Etiology, Symptomatology and Treatment of Tubal Pregnancy, Acta obst. & gynec. Scandinav. 16: 509, 1936.

In the Gynecological Clinic at Upsala, 111 cases of tubal pregnancy were treated during the years 1924 to 1934. In no less than 47 out of 97 married patients, five years or more had elapsed before conception took place, pointing to the occurrence of factors impeding conception in a large number of cases.

Follow-up of a large number of women with salpingo-oophoritis who had had conservative treatment, and of women with febrile abortions, showed that salpingitis does not lead to tubal pregnancy in any considerable number of cases, the cause being probably more frequently found in adhesions around the tubes caused by small intraperitoneal hemorrhages from the adnexa.

Signs of pregnancy were observed in 97 cases (87.4 per cent). Internal hemorrhage accompanied by symptoms of shock was present in 45 (40.5 per cent). In 91 cases (82 per cent), external hemorrhage was found, being sparse and dark colored in 76.

Operation seems to be indicated not only in cases showing internal hemorrhage with severe symptoms but also in other cases on account of the danger of tubal rupture, infection of hematocele, and risk of the other tube becoming incapable of performing its functions because of formation of adhesions.

Fifty-seven patients were followed up for at least three years. Of 51 patients with a capacity for conception who had not avoided conception, 9 (17.6 per cent) had an intrauterine pregnancy. Out of 9 patients on whom salpingostomy on the remaining tube was performed, 7 remained sterile and 2 developed another tubal pregnancy.

J. P. GREENHILL

Items

American Board of Obstetrics and Gynecology

Application for admission to the Group A, May, 1939, Board examinations must be on file in the Secretary's Office not later than March 15, 1939.

The general oral, clinical and pathological examinations for all candidates, Part II examinations will be held as follows: Group A, Saturday and Sunday, May 13 and 14; Group B, Monday and Tuesday, May 15 and 16, immediately prior to the Annual Meeting of the American Medical Association, at St. Louis, Missouri. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Candidates for re-examination in Part II (Groups A and B), must request such re-examination by writing the Secretary's Office before March 15, 1939. Candidates who are required to take re-examinations must do so before the expiration of three years from the date of their first examination.

The annual dinner meeting of the Board, to which all Diplomates and Candidates are invited, as well as wives and others interested in the work of the Board, will be held on Wednesday evening, May 17, following the close of the examinations.

The dinner meeting will be in the Tower Room of the Congress Hotel, St. Louis, at 7:00 P.M. (informal). Price $2.50 per plate. You may obtain tickets from Dr. Joseph L. Baer, 104 S. Michigan Ave., Chicago, Ill. Speaker: Dr. Robin C. Buerki, Director, Commission on Graduate Medical Education of the Advisory Board for Medical Specialties; topic: "The Value of Certification."

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Royal College of Obstetricians and Gynecologists

It is of interest to note that by Royal Command the title of "Royal" has been granted by H. M. the King to the British College of Obstetricians and Gynecologists. This action may be regarded as setting the seal of approval upon an institution which has occupied a position of increasing importance in English medicine. The membership of the College is at present over 600 and a diploma is issued only to those qualified by a long period of resident training in the specialty and after adequate examinations.

American Journal of Obstetrics and Gynecology

VOL. 37 MAY, 1939 NO. 5

Central Association of Obstetricians and Gynecologists

PELVIC PAIN*

ROBERT D. MUSSEY, M.D., ROCHESTER, MINN.
(From the Mayo Clinic)

THE subject of pelvic pain is extensive and important but there is comparatively little reference to it in most books on gynecology. Pain is the symptom which most commonly causes the patient to seek the physician for advice and relief. Pain always concerns the physician, because in its various manifestations it presents the dual problem of interpretation and treatment.

To a large majority of the laity and in the past, at least, to some physicians, mention of pain or discomfort in the region bounded by the pelvic girdle has indicated some disorder of the organs of reproduction. Within the memory of many physicians now living persistent complaint of pain in the region of the ovaries meant almost certain removal of one or both of these organs. Fortunate, indeed, was the young woman suffering from severe dysmenorrhea, who arrived at full maturity still possessed of her ovaries. Even at the present time, occasionally, the gynecologist is consulted by women who have had one and later the other ovary removed for "ovarian pain." An astonishingly large number of bodily discomforts and pains have been attributed to disease of the pelvic organs. Woman has been described as a "frail creature with a headache and pain in the back." Thanks to the emancipation of woman from the confines of garments of the Victorian age and from conventionalities which prevented her from participating freely in healthful physical exercise, she is no longer a frail creature. Headache may be less prevalent and some of the backache may be gone but there is still enough of the latter, often attributed to a pelvic lesion,

*Presidential address read at Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., Oct. 6 to 8, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

to try all the diagnostic acumen and therapeutic ability of the physician. Not only does one deal with patients who have pelvic pain caused by a demonstrable lesion of the pelvic viscera but one also encounters complaints of pelvic pain by patients whose pelvic organs do not reveal any abnormality.

Relief of pain is necessary and the investigation of the source of pain often presents a most intriguing problem. The cause of pain, its manner of production, its anatomic pathways, its physiology, variations in its intensity, and its manifestations to the conscious mind have all undergone careful scrutiny by anatomists, physiologists, psychiatrists, practitioners of medicine, and even by medical philosophers. Yet in spite of theories, in spite of study and investigation, practitioners of gynecology are confronted too often with patients whose complaint of pain does not conform to the various familiar syndromes of dysfunction or disease of the pelvic organs. Occasionally such pain is not susceptible of diagnosis and may fail to respond to various therapeutic and even operative procedures.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

To advance understanding of the subject of pelvic pain it is logical to consider the anatomy and physiology concerned. Further information may be gained by an attempt to evaluate the various complaints of pelvic pain for which women have consulted a gynecologist. In order to accomplish this, the data from a group of records will be reviewed after the anatomy and physiology of the pelvic nerve supply have been discussed. It is hoped that a consideration of the combined academic knowledge of pelvic pain and its practical features may enhance understanding of this subject.

In considering the subject of pelvic pain it is necessary to discuss the manner in which pain arises and the manner in which it reaches the consciousness of the individual. It is also necessary to consider the individual's nervous system and physical development; heredity, environment, tendencies and so forth are all a part of the picture. In many cases asthenic development or constitutional inferiority is a major factor. Yet one may not assume that pain is functional because the patient has an unstable nervous system. Also, when such a patient has more or less evident pathology in the pelvic organs, evaluation of the degree of pain and other symptoms may be most difficult.

To define pain is difficult. To say that pain is a more or less severe sensation of discomfort, requires amplification. Pain may be described as a sensation which informs the sufferer either that he has been subjected to some external stimulus which is dangerous to his well-being or as a sensation which informs him that his body is not functioning in its normal manner. In considering pelvic pain the physician is concerned with painful stimuli carried both by the somatic or voluntary nervous system and the visceral nervous system, which is variously called the autonomic or the sympathetic-parasympathetic nervous system. The autonomic nervous system, which maintains the internal physiologic adjustments necessary to life, is automatic and involuntary in its action.

A review of the literature on the physiology and anatomy of visceral pain, as it applies to pelvic pain, reveals many controversial points and, in this presentation, no attempt will be made to give a detailed bibliography. The reader is referred to the monographs of Livingston and White and articles by Davis and Hamilton which give comprehensive discussions and reviews of the literature concerned. An attempt will be made to limit this discussion to those facts and theories which appear to have the most scientific basis, rather than to review the opinions expressed by many different authors.

In common with other viscera, the pelvic organs receive most of their nerve supply from the autonomic nervous system. Efferent fibers emerge from the anterior roots of the thoracic and lumbar portions of the spinal cord. These fibers pass to the corresponding ganglia of the lateral sympathetic chains to join fibers from higher portions of the cord. From the sympathetic ganglia fibers emerge to form the various plexuses and their connections; from these plexuses fibers pass down in front of the spinal column and furnish innervation to the abdominal viscera. Branches from the solar plexus, uppermost of these abdominal plexuses, pass downward to form, in turn, the superior mesenteric plexus and the inferior mesenteric plexus. Fibers from the lateral portion of the inferior mesenteric plexus proceed downward and supply the distal portion of the colon, the upper part of the rectum, ovaries, and tubes. The major portion of the fibers from the inferior mesenteric plexus unite anteriorly and are joined by fibers from the four lumbar sympathetic ganglia to form the superior hypogastric plexus (the presacral nerve or plexus), which lies below the bifurcation of the aorta and in front of the sacrum. Through the hypogastric plexus pass almost all of the nerve fibers which innervate the pelvic viscera, the nerve supply to the ovaries and distal portions of the tubes being the notable exceptions. The right and left inferior hypogastric nerves, arising from the anterior portion of the presacral plexus, pass down deep into the cul-de-sac to enter the pelvic ganglia, which innervate the uterus; fibers from the lateral portion of the hypogastric plexus form the periureteral plexus, from which vesical and ureteral nerves arise, as well as a few fibers for the uterus and vagina. The course of fibers from the pelvic ganglia which innervate the uterus will not be described in detail; it may be well to state that there is no macroscopic anastomosis between the nerves of the two sides of the uterus or between these nerves and the nerves to the ovaries. Other uterine nerves, which spring from the upper part of the anterior border of the hypogastric plexus, accompany the uterine artery. At the middle of the body of the uterus, these fibers divide into three branches, two of which finally enter a small ganglion the size of a grain of corn situated in an angle between the tube and uterus. Nerves from this ganglion supply the broad ligament, mesosalpinx and inferior portion of the tube; these fibers follow both the uterine and ovarian branches of the ovarian artery but do not reach the ovary. Some fibers from the thoracic as well as the lumbar sympathetic nerves pass down through the solar, mesenteric and hypogastric plexuses and are included

in the nerve supply to the various pelvic organs. This will serve to explain some of the distant pain and other widespread symptoms associated with pelvic dysfunction or disease.

As an example of the intercommunication of sympathetic fibers from the various plexuses, I will relate the case of a highly nervous woman, an air swallower, who came under my care some twelve years ago. During the second stage of labor she swallowed sufficient air to make visible the distention of the stomach above the uterine fundus. When the stomach became distended the patient complained of epigastric discomfort and the labor pains ceased. Intubation of the stomach to release the air was followed by resumption of uterine contractions. Repeatedly she swallowed air and, as labor pains ceased, it became necessary to intubate her stomach three times before the baby was delivered.

The parasympathetic nerve supply to the pelvic viscera arises from the sacral segments of the spinal cord. These parasympathetic fibers accompany the pelvic nerves ("nervi erigentes") to the pelvic ganglia and from there supply the pelvic viscera. Probably the parasympathetic nerves are the evacuatory nerves of the uterus.

Afferent fibers or sensory sympathetic nerves pursue a course similar to the efferent fibers with the exception of a detour through the posterior roots to the spinal cord. It may be said, in passing, that there has been a great deal of discussion as to the actual presence of afferent or pain-conducting sympathetic sensory fibers. Langley and Anderson were chiefly responsible for the idea that there were no sensory nerves coming from the pelvic viscera. However, there is histologic evidence that, in the sympathetic fibers under discussion, there are present myelinated nerve fibers which are identical with cutaneous sensory nerves. There is abundant clinical evidence that various types of neurectomy relieve many types of visceral pain. Both of these facts point to the presence of actual sensory or afferent fibers among the sympathetic fibers. Other explanations for the relief of pain by severance of the sympathetic pathways have been propounded. Among these is the hypothesis that the pain is relieved by the vasodilatation which is due to the interruption of the sympathetic nerve supply.

Discussion of the physiology of the sympathetic nervous system includes consideration of motor, vasomotor, sensory, and glandular functions. This subject is controversial, and in this discussion of pelvic pain an attempt will be made to limit the remarks to that function of the pelvic sympathetic structures which is concerned with visceral pain. At present most authorities accept two types of visceral pain, direct pain and referred pain, both from a visceral stimulus. As previously noted, early authors denied the possibility that there could be such a thing as pain coming directly from a viscus. All pain arising from a visceral source was explained on the basis of referred pain. Head made the interesting suggestion that the internal organs have not developed a sense of localization, such as that of the skin, so that the maximal effect of disturbance may not be felt in the organ affected, but is conducted to that portion of the cord from which its sympathetic nerves are given off, sets up an irritability in that segment of the cord and from there is

distributed as pain or discomfort to the cutaneous areas served by that segment of the cord. Mackenzie stated, in brief, that when unusual stimuli are received in the spinal cord from a viscus, they create an "irritable focus" in the spinal cord which causes other impulses received at that level from a somatic source to be exaggerated. The viscero-cutaneous or irritable segment hypothesis explains hyperalgesia, sweating, erection of hair, vascular changes, muscle spasm, and often, intense superficial pain, associated with visceral disease. Mackenzie's theory is all right as far as it goes but he did not recognize, as did Head, the now accepted fact that there is another type of pain which comes direct from the viscera.

The following comment may be made about direct visceral pain. A certain type of stimulus must be present to produce direct visceral pain. Viscera are insensitive to ordinary stimuli but are sensitive to adequate stimuli which arise from forces which threaten to interrupt ordinary physiologic processes. Such adequate physiologic stimuli are rapid distention or vigorous contraction of hollow viscera, rapid stretching of the capsule of a solid viscus; overdistention, crushing or stretching of blood vessels, and anoxemia of functioning muscular tissue. The fact that these adequate physiologic stimuli do exist has been proved experimentally and by clinical observation. That they give rise to a direct pain which is entirely different from referred pain appears to be an accepted fact. Direct pain also may result from irritation of the nerve root or inflammation of the ganglia.

Even with combined reflex and direct sympathetic nerve response to pain, the pelvic organs remain relatively insensitive to pain. Morley emphasized the fact that most of the sensation of pain from visceral lesions is due to the somatic pain produced by stretching, injury, or inflammation of the peritoneum. Mention has been made previously that diagnosis of the cause of pain and evaluation of its degree frequently must take into consideration intangible factors as well as pathologic changes in the viscera. For instance, the pain caused by a lesion of a pelvic organ may be quite localized, at first, but if the patient becomes anemic, exhausted from the disease, or is under nervous or mental strain, the pain may become of a more generalized nature until it finally may have no apparent relation to the affected organ. When such conditions obtain, treatment and even cure of the local condition may not relieve the patient of pain until the physical and nervous exhaustion are relieved. Patients who complain mostly of chronic, more or less widespread, pain are likely to have functional rather than structural disorders. Certain cases of uterine or ovarian pain, so-called visceralgia, are perhaps psychic in origin. Sometimes violent emotions are followed, not only by vascular contraction of the surface vessels but also by contraction of the vessels of the internal organs, giving rise to sensations of pain. However, pain and discomfort may result from panniculitis in the obese, from tetany-like contractions associated with low calcium content of the tissues or, as mentioned previously, from nerve root irritation or from inflamed nerve ganglia. In the absence of

evidence of organic disease, therefore, one should be cautious in attributing complaints of pain to nervous exhaustion or psychalgia.

With the assistance of Dr. Robert B. Wilson, Fellow in Obstetrics and Gynecology of the Mayo Foundation, an analysis has been made of case records of women whose chief complaint was pain or discomfort in the pelvis. It was decided to use two avenues to approach the subject of pelvic pain: first, to make a statistical analysis of the frequency and location of pelvic pain at various ages, and the relation of these three conditions to the final diagnosis; second, to scrutinize such histories from a clinical viewpoint, with the intention of describing certain characteristics of pelvic pain, which do not permit easily of statistical review.

STATISTICAL ANALYSIS

In order to obtain proper sampling of cases for the statistical review, it was decided to pull at random, from the files of the Mayo Clinic, case records of women who had passed the age of fifteen years and who were registered as patients in 1936. The records of 3,096 women were reviewed, without attention to civil state, in the selection of 500 cases in which complaint was made of pelvic pain. These records were analyzed for the patient's age, site and frequency of pain of which the patient complained primarily, site of secondary pain, complaints of pain in multiple or more than two sites, and occurrence of dysmenorrhea as the primary complaint. Arbitrarily, there were selected four sites of pelvic pain, as follows: lumbosacral region, generalized lower abdominal pain, lower right abdominal quadrant, and lower left abdominal quadrant (Table I).

Because many patients complain of pain in more than one site, a table was made showing the number and percentage of primary and secondary complaints (Table II). The final diagnoses in the 500 cases were grouped in order of frequency. Since in some cases there was more than one diagnosis, it follows that more than 500 diagnoses were charted. In Table III is given the frequency of various diagnoses shown as percentage of patients who complained of different types of pelvic pain. In Table IV is shown the frequency of various diagnoses, as number and percentage of patients who complained of pelvic pain in three age ranges, each inclusive; these are, first, 15 to 34 years, the ages in which acute conditions are most common; second, 35 to 49 years, the menopause and near menopause group; and third, those patients 50 years of age and older, the postmenopause group.

These data will not be discussed in detail. However, there are several observations of interest, most of which serve to affirm clinical impressions. The number of records reviewed, 3,096, is sufficient to justify the statement that among women patients, 500 or approximately one-sixth, consulted physicians for ailments concerned with pain in the region of the pelvis (Table I). As these case records were picked at random from the general file, it follows that a much higher percentage of those coming under the observation of a gynecologist would complain of pelvic pain. Dividing the 3,096 patients by decades, and one-half decade, of age, it is noteworthy that pain in the region of the pelvis was

TABLE I. FREQUENCY OF PATIENTS, AT VARIOUS AGES,* WHO COMPLAINED OF PELVIC PAIN

COMPLAINT	AGE, YEARS															
	15 TO 19		20 TO 29		30 TO 39		40 TO 49		50 TO 59		60 TO 69		70+		ALL AGES	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Pain with menses			17	3.8	16	2.0	9	1.1							42	1.4
Backache			10	2.2	25	3.2	26	3.2	16	2.8	9	2.8	1	1.4	87	2.8
Pain lower left quadrant	1	1.1	8	1.8	23	2.9	13	1.6	3	0.5	3	0.9			51	1.6
Pain lower right quadrant	9	10.3	40	8.9	32	4.1	24	2.9	13	2.3	4	1.3	1	1.4	123	4.0
Generalized lower abdominal pain	6	6.9	31	6.9	47	6.0	40	4.9	12	2.1	9	2.8			145	4.7
Multiple complaints	4	4.6	11	2.5	17	2.2	13	1.6	4	0.7	3	0.9			52	1.7
Total	20	23.0	117	26.2	160	20.3	125	15.2	48	8.5	28	8.8	2	2.8	500	16.2
Patients of entire series (with and without pelvic pain)	87		447		789		821		563		317		72		3096	

*The percentages are based on the number of patients with and without pelvic pain in each age group. For instance of the 3096 patients surveyed, 447 were in the age range 20 to 29 years; of these 17, or 3.8 per cent, complained of pain with menses.

of more frequent occurrence in the lowest three age groups and of less frequent occurrence in each succeeding decade (Table I). More women between the ages of 30 and 50 years consulted physicians because of various ailments than did women of any other two decades; this accounts for the fact that more than half of the 500 patients with pain in the pelvic region were in these two decades.

TABLE II. FREQUENCY OF PRIMARY AND SECONDARY COMPLAINTS

COMPLAINT	TOTAL PATIENTS		PATIENTS WITH PRIMARY COMPLAINTS		PATIENTS WITH SECONDARY COMPLAINTS	
	NUMBER	PER CENT*	NUMBER	PER CENT†	NUMBER	PER CENT†
Backache	87	17.4	62	71.3	25	28.7
Generalized lower abdominal pain	145	29.0	120	82.8	25	17.2
Pain lower right quadrant	123	24.6	106	86.2	17	13.8
Pain lower left quadrant	51	10.2	45	88.2	6	11.8
Pain with menses	42	8.4	30	71.4	12	28.6
Multiple complaints	52	10.4	43	82.7	9	17.3
Total	500	100.0	406	81.2	94	18.8

*Based on total number of 500 patients who complained of pelvic pain.
†Based on the total number of patients with each particular complaint.

Study of the figures in Table II shows that when backache occurred it was a primary complaint in 71.3 per cent of the cases and a secondary complaint in 28.7 per cent, the most frequent of the secondary complaints. As would be expected, 63.8 per cent of the patients complained of lower abdominal pain, the number having pain in the right lower quadrant being greater than the number having pain in the left lower quadrant, owing to the relative frequency of appendicitis.

Many diagnoses were encountered (Tables III and IV). Fourteen are listed, the last being "cause undetermined"; the unlisted diagnoses, 20 per cent of the whole, including a variety of conditions, are designated as "all other diagnoses." Among the listed diagnoses it is of interest to note that the first eight, in order of frequency, are chronic nervous exhaustion, pelvic inflammatory disease, lumbosacral pathologic conditions, appendicitis, ovarian cysts, uterine myomas, dysmenorrhea and constipation. The difficulty of establishing a definite diagnosis for pelvic pain in many instances is illustrated by the fact that no organic cause for the pain was found in approximately 25 per cent of the group under the diagnoses of "chronic nervous exhaustion" (17.6 per cent) and "indeterminate" (7.8 per cent). Pelvic inflammatory disease (17 per cent), which was the greatest single organic cause of pelvic pain, was relatively common and occurred with almost equal frequency in the first two age groups and quite infrequently in the third age group (Table IV).

Pathologic change in the lumbosacral region (Table IV) was next in frequency (13.8 per cent); this condition was relatively infrequent up to the age of 35 years, becoming more common as age increased until 24.4 per cent of those who were more than 50 years of age had a diagnosis of some pathologic condition in this region. It was not surprising

TABLE III. FREQUENCY OF VARIOUS DIAGNOSES AS PERCENTAGE* OF PATIENTS WHO COMPLAINED OF DIFFERENT TYPES OF PELVIC PAIN

DIAGNOSIS	COMPLAINT						
	ANY PELVIC COMPLAINT	BACKACHE	GENERALIZED LOWER ABDOMINAL PAIN	PAIN LOWER RIGHT QUADRANT	PAIN LOWER LEFT QUADRANT	PAIN WITH MENSES	MULTIPLE COMPLAINTS
Chronic nervous exhaustion	17.6	21.8	12.4	9.8	23.5	26.2	30.8
Pelvic inflammatory disease	17.0	4.6	29.7	8.9	25.5	14.3	15.4
Lumbar or sacral pathologic condition	13.8	65.5					23.1
Appendicitis	13.6	1.1	9.0	35.0	11.8	4.8	5.8
Ovarian cysts	12.4	2.3	15.9	13.8	15.7	11.9	13.5
Uterine myomas	11.0	9.2	13.1	8.9	9.8	14.3	11.5
Dysmenorrhea	8.4			4.9		69.0	13.5
Constipation	8.4	3.4	7.6	9.8	13.7	4.8	13.5
Retroversion	7.2	8.0	4.1	6.5	9.8	4.8	15.4
Cervicitis	7.2	4.6	9.7	2.4	7.8	11.9	11.5
Relaxation	5.4	4.6	10.3	3.3			7.7
Carcinoma	3.2	4.6	4.1	0.8	3.9	2.4	3.8
Endometriosis	2.6		2.8		5.9	7.1	3.8
Indeterminate	7.8		9.0	8.9	19.6		9.6
All others	20.4	21.8	20.0	24.4	25.5	11.9	11.5
Actual number of patients with pelvic pain	500	87	145	123	51	42	52

*The percentages are based on the number of patients who made each type of complaint; for instance, 87 patients complained of backache and of these 19, or 21.8 per cent, received a diagnosis of chronic nervous exhaustion; 8 or 9.2 per cent received a diagnosis of uterine myoma. A patient may receive more than one diagnosis. Therefore, the percentages add to more than 100.

TABLE IV. FREQUENCY OF VARIOUS DIAGNOSES, SPECIFIC FOR AGE, AS NUMBER* AND PERCENTAGE* OF PATIENTS WHO COMPLAINED OF PELVIC PAIN

DIAGNOSIS	ALL AGES		15 TO 34 YEARS		35 TO 49 YEARS		50 + YEARS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Chronic nervous exhaustion	88	17.6	39	18.1	37	17.9	12	15.4
Pelvic inflammatory disease	85	17.0	44	20.5	38	18.4	3	3.8
Lumbar or sacral pathologic condition	69	13.8	19	8.8	31	15.0	19	24.4
Appendicitis	68	13.6	47	21.9	15	7.2	6	7.7
Ovarian cysts	62	12.4	30	14.0	29	14.0	3	3.8
Uterine myomas	55	11.0	13	6.0	38	18.4	4	5.1
Dysmenorrhea	42	8.4	29	13.5	13	6.3		
Constipation	42	8.4	17	7.9	17	8.2	8	10.3
Retroversion	36	7.2	21	9.8	15	7.2		
Cervicitis	36	7.2	9	4.2	21	10.1	6	7.7
Relaxation	27	5.4	5	2.3	14	6.8	8	10.3
Carcinoma	16	3.2	2	0.9	7	3.4	7	9.0
Endometriosis	12	2.6	7	3.3	5	2.4		
Indeterminate	39	7.8	19	8.8	16	7.7	4	5.1
All others	102	20.4	29	13.5	46	22.2	27	34.6
Total diagnoses	779		330		342		107	
Actual number of patients with pelvic pain	500		215		207		78	

*The percentages are based on the number of patients of the ages specified who complained of any type of pelvic pain. For instance, there was a total of 215 patients of the ages 15 to 34 years who complained of pelvic pain; of these, 39 or 18.1 per cent, received a diagnosis of chronic nervous exhaustion. A patient may receive more than one diagnosis. Therefore, the "number" columns total to more than the actual number of patients represented and the percentages add to more than 100.

to find that ovarian cysts were found slightly more frequently in the presence of pelvic pain than were uterine myomas, and also that more ovarian cysts were diagnosed among younger than among older women. The probability of malignancy associated with pelvic pain was less than 1 per cent in the age range of 15 to 34 years, inclusive; was increased with advancing age to about 3 per cent in the middle age range and was 9 per cent among women more than 50 years of age who complained of pelvic pain.

CLINICAL ASPECTS

These data, showing the relative frequency of pain in various regions of the pelvis at various ages, are of considerable interest. Discussion of certain symptoms of pelvic pain not so amenable to statistical review should have additional value.

It is not proposed in this discussion to attempt to distinguish, by means of the description of painful symptoms, the various diseases and dysfunctions of the pelvic organs. However, there are certain characteristics of pain which will be described; namely, the relation of pain to the organ or tissue in which the painful stimulus arises, the avenue by which this stimulus reaches the consciousness of the individual and the localization by the individual of the painful sensation.

The most definitely diagnostic type of pelvic pain is probably somatic pain which is produced by an irritative stimulus applied to the parietal peritoneum. The intensity of pain accompanying peritonitis lessens or stops when the friction of inflamed surfaces ceases, as for example, in cases of general peritonitis with accompanying paralysis of intestinal peristalsis and splinting of muscles of the abdominal wall. Peritoneal pain reaches the consciousness of the individual as directly as a painful stimulus applied to the surface of the body and accordingly the site of the sensation of pain is localized by the individual usually directly at the site of the irritation. For example, the pain of acute gonorrheal pelvic inflammatory disease is chiefly a peritoneal pain, either the result of stretching of the peritoneal covering of the structures involved or the result of local peritonitis. Similarly, the earliest pain to be noted in tubal pregnancy accompanies stretching of the peritoneal covering by distention of the tube or is owing to the irritation of blood leaking from the fimbriated end. The pain accompanying acute rupture of the Fallopian tube is sudden and severe and is usually definitely localized. Very infrequently the pain accompanying an acute pelvic lesion may be referred to upper portions of the abdomen through strands of sympathetic nerve fibers which have followed the sympathetic chain from higher segments of the cord. Pain and other symptoms caused by torsion of the pedicle of an ovarian or uterine tumor produce a combination of at least two types of pain: first, localizing pain due to peritoneal injury and, second, a diffuse type of pain caused by disturbance of circulation in the tumor and accompanied by reflex gastrointestinal symptoms, such as vomiting. These disturbances reach the consciousness of the individual through the reflex and perhaps the direct pathways of the sympathetic nervous system.

The acuteness, degree and accuracy of localization of pain produced by irritation of the peritoneum covering part or all of a viscus depend on the extent of movement and the rapidity of change in volume which the viscus must make in carrying on its function. It is evident that irritative lesions affecting the peritoneum which overlies the bladder or the rectum are commonly accompanied by pain whenever a sudden change occurs in the size of the viscus, such as that produced by evacuation or sudden distention. Due to its location in the pelvis the peritoneum overlying the rectum is subjected to more insults than any other portion of the pelvic peritoneum. For this reason pain or discomfort localized in the region of the rectum is not infrequently a subject of complaint; it commonly occurs in the presence of inflammatory conditions in the pelvis; in cases such as tubal pregnancy, or ruptured hemorrhagic ovarian cysts, accompanied by the deposit of blood in the cul-de-sac; as a consequence of the cyclic recurring irritation of endometrial implants, and as a result of adhesions which are stretched during physiologic activity of the rectum. Similar causes are responsible for certain cases of dyspareunia. Chronic adhesions in the pelvis, per se, are not responsible for pain unless the peritoneum involved in the adhesions is stretched by movement of the viscus, such as that produced by its functional activity, by physical activity of the individual, or by the manipulation of physical examination.

Although pain of peritoneal origin is a common symptom of acute gonorrheal salpingitis, it is less noticeable in pelvic inflammation associated with thrombophlebitis or cellulitis, because these inflammations, especially the former, are not so frequently associated with localized peritonitis. Little or no pain is associated with inflammatory lesions of the uterine cervix unless there is involvement of the parametrial tissue, the sacrouterine ligaments or the broad ligaments. When pain is evident in this condition, it usually accompanies activity, such as walking, defecation, etc. Similarly, metritis or endometritis is not accompanied by much direct pain but can be responsible for a severe, referred type of pain during contractions of the uterine muscles.

Benign or malignant tumors of the uterus and ovaries do not ordinarily cause pain. When such tumors are accompanied by pain it becomes evident that some unusual complication has occurred which has produced peritoneal irritation or stretching, or which has interfered with the motor function of a pelvic viscus. The pain which ordinarily accompanies carcinomatous involvement of the broad ligament is of constant, deep, boring character.

Mention has been made previously that the sympathetic nerve supply of the ovaries is entirely separate from that of the uterus and that the ovaries have no somatic sensory nerve supply. Many patients complain of pain in the region of an ovary, but it is often extremely difficult to assign the pain to ovarian pathologic change. True ovarian pain is perhaps relatively uncommon; it is usually mild and diffuse but can be severe. Ovarian pain would appear to be caused chiefly by stretching of the capsule and partly by disturbance of the circulation or tension on structures which support the ovary or by inflammation of these structures.

Malposition of the uterus and other pelvic organs may or may not be accompanied by discomfort and rarely by acute pain. Dull pain in the pelvis, sense of weight, bearing down, backache and aching in the thighs and groin associated with malposition of pelvic organs are due partly to stretching of supporting fibrous tissue and partly to reflex pain resulting from tension on blood vessels and the sympathetic nerves which accompany them. Promise of relief of discomfort by operations for restoring the position of organs must be guarded. In many instances retroversion or even complete prolapse is unaccompanied by discomfort and many women whose pelvic organs are in normal position may relate all of the symptoms of discomfort noted above.

Backache of women is commonly supposed by the laity to be due to some pelvic disorder. It is true, in many cases, that pelvic lesions are the source of pain referred through the sympathetic nervous system to the sacral, lumbar or even the lower thoracic regions. In even more cases backache arises from conditions or lesions affecting the spine or its supporting structures. In fact in not a few cases discomfort in the anterior portion of the pelvis may be referred from structural strain in the back or even from a lesion affecting the spinal cord or its posterior sensory nerve roots.

The pain and discomfort associated with so-called functional dysmenorrhea are probably the best example of pelvic pain which reaches the consciousness of the individual through the sympathetic or autonomic nervous system. There is reason to think that this type of dysmenorrhea is caused by a hypertonicity of the uterine musculature with accompanying ovarian dysfunction. In attempting to determine whether dysmenorrhea is functional, one must bear in mind other conditions which may cause dysmenorrhea, such as maldevelopment or malposition of the uterus, pathologic lesions in the pelvis, or any condition which may obstruct menstrual flow. One or more of these conditions may complicate functional dysmenorrhea and are mentioned to emphasize the difficulty of correctly diagnosing this condition. It is particularly important to determine correctly the cause of dysmenorrhea because of the increasing frequency of operations for resection of the presacral nerve or plexus, performed for the relief of persistently severe dysmenorrhea.

SUMMARY

The subject of pelvic pain has been considered from three angles:

1. The anatomy and physiology of the nerve supply to the pelvic viscera have been described briefly.

2. A statistical study has been made of the case records of 500 women who sought medical relief because of pelvic pain.

3. Certain features of pelvic pain have been related from the point of view of clinical observation.

It is hoped that at least some information obtained from this discussion of pelvic pain may add to the knowledge and perhaps serve to improve diagnostic accuracy in the presence of this frequently encountered and interesting symptom.

COLLAPSE THERAPY FOR TUBERCULOSIS IN PREGNANCY*

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THE problem of pregnancy and tuberculosis is not yet a settled one as is evidenced by the constantly growing literature on the subject. In the past, opinion, for the most part, has been divided between two extremes. Some authorities held that tuberculosis, especially in the active forms, was so frequently made worse by pregnancy as to offer an absolute indication for therapeutic abortion. Others, and these were in the minority, were just as convinced that childbearing had at most a negligible effect on the outcome of the pulmonary disease. To the unbiased observer, it would seem that neither view is based on entirely sound data and reasoning, or indeed is free of pure speculation and prejudice.

Recent trends have been toward an intermediate position. Although it is realized that pregnancy and delivery are always potential threats to the pulmonary disease, it is equally true that the danger varies greatly with conditions. Indeed, in many instances the circumstances may be such as to involve little risk. Consequently, the procedure in each case should be determined by an appraisal of the probable effects of such factors as duration of pregnancy, parity, and type of tuberculous lesion. Of greatest importance in this respect, and often the deciding point, is the availability of efficient treatment for the tuberculosis.

With the establishment of the value of collapse therapy in tuberculosis, this treatment was early proposed for and subsequently used to some extent in pregnant tuberculous women. One may find occasional reports (since 1906) concerning single cases or small series. In recent years these have been so generally favorable as to make one suspect that too often only the good results have been published. Of much more importance are a few reports of larger series. These we have been able to find only in the foreign literature. The following are studies published in the last decade which concern twenty or more cases:

Roloff reported 70 cases with artificial pneumothorax and spoke highly of the procedure in pregnancy. However, he presented no statistics or statements as to the exact results.

*Drs. Seeley, Siddall and Balzer were awarded the annual prize for the best clinical paper submitted by members of the Central Association of Obstetricians and Gynecologists, during the year 1938. This paper was read at the meeting held in Minneapolis, Minn., October 7, 1938.

Binet, in addition to giving the outcome in 57 cases, suggested theoretical objections to artificial pneumothorax in pregnancy. For instance, with the additional load of pregnancy, would not the sudden collapse reduce the pulmonary circulation and oxygenation to the point of harmful asphyxia? Could not sudden restriction of the field for blood oxygenation throw a load on the right heart, already extended by pregnancy, beyond its reserve? Might not the digestive disturbances frequently occurring with pulmonary collapse plus those of late pregnancy necessitate interruption of the treatment? He answers that these possibilities are practically nonexistent. Of his 57 patients, 5 died, 9 were worse, and 43 were improved or at least not harmed. Somewhat better results were obtained in those becoming pregnant in the course of treatment than among those in whom tuberculosis became evident during pregnancy. He also included 5 instances of therapeutic abortion and artificial pneumothorax with good results. It is regrettable that there was no definite statement as to the duration of treatmen and observation post partum.

Migliavacca reported the results in 26 cases with artificial pneumothorax and phrenic nerve operation. Over one-third were classified as having far advanced (Turban III) lesions. It is to be noted that 10 were treated by therapeutic abortion as well as collapse. One aborted spontaneously, 2 delivered prematurely, and 13 at term. After a year 75 per cent of the entire group were improved, 10 per cent worse, and 15 per cent dead. Among those without therapeutic abortion, there were 3 deaths, a mortality of 19 per cent.

Rist and Jottras divided their cases into two series. Those in the first group became pregnant in the course of collapse treatment, and those in the second had pneumothorax started sometime during pregnancy. In the first series of 58 women there were 13 deaths within two years after delivery; 7 were worse or unimproved; while 38 or 65.6 per cent had favorable results. Where collapse therapy was started during pregnancy, there were only 33 out of 74 (45 per cent) with good results. In general, the earlier artificial pneumothorax was begun, the more favorable was the outcome. Rist and Jottras contend that their figures demonstrate a definite ill effect of pregnancy on tuberculosis, but believe that collapse therapy considerably diminishes the indications for therapeutic abortion.

Praloran's 80 patients were given collapse therapy principally by artificial pneumothorax, phrenic nerve operation, or by both. His statistical study is apparently restricted to pregnancy, labor and, in some cases, the puerperium up to a maximum of two months. During this limited time 2 patients died, 3 were worse, and 12 unimproved. Collapse therapy had little effect on pregnancy, as only 2 aborted and 6 had premature labor. He believed that the premature labors were due to progression of the disease rather than collapse therapy, as all 6 mothers either died or became worse. The 72 babies born at term weighed between 3,000 and 4,000 gm. for the most part.

It can be seen from these reports that, in spite of various enthusiastic opinions, the result of collapse in pregnancy is not uniformly favorable. Obviously, this is to be expected with such a serious disease as tuberculosis. However, inasmuch as collapse therapy has been proposed as a welcome substitute (at least to some extent) for therapeutic interruption of pregnancy, we should like to know more specifically to what degree the effect of pregnancy can be ameliorated. In regard to this point, we have been unable to find any good comparison of results for pregnant patients with and without collapse therapy. Among other desirable but insufficient data are (1) more information regarding the results in different types and grades of pulmonary involvement, and (2) further knowledge of the effect of this treatment on pregnancy.

The material at Herman Kiefer Hospital offers an unusual opportunity for the study of the effects of pregnancy on tuberculosis and of tuberculosis on pregnancy, with particular reference to the influence of collapse therapy. The patients studied were delivered on the obstetric service and were all treated for their pulmonary condition on the tuberculosis division of the same hospital. During the period covered by our investigation there was only one interruption of pregnancy for tuberculosis. This permits a comparison of results which for practical purposes is uncomplicated by consideration of therapeutic abortion.

MATERIAL

During the seven years (1930 to 1936) covered by our study, there were delivered a total of 109 tuberculous women who received adequate treatment for at least one year after delivery or died while under medical care during that time. It was thought that this period would be suitable for the recognition of the effects of childbearing on the tuberculosis. Fifty-four of these patients were in the hospital for not less than two months before delivery, and received collapse therapy during this time. Twenty-two had phrenic nerve operations, 21 artificial pneumothorax, and 11 both. (For various reasons, pregnancy after thoracoplasty was not considered here but will be investigated separately.) Eleven women were hospitalized for a sufficient period before term (at least two months) to permit collapse therapy, but they either refused this treatment, or it was considered to be unnecessary or unsuitable for the pulmonary condition. The remaining 44 patients were in the hospital for less than two months ante partum, or were treated through the outpatient service only, or were first seen as obstetric patients at labor, and had received little or no treatment for their tuberculosis. All of the 109 women were transferred to the tuberculosis service seven to ten days after delivery, where they received the treatment indicated in the opinion of the phthisiologists. In many instances this included collapse therapy. We have for comparison then, three groups of patients with the same adequate care post partum, but differing widely in the type of treatment given before delivery.

In a comparison of the results for obstetric patients with tuberculosis, a knowledge of the nature (extent and character) of the pulmonary lesions in the different groups is essential. All of our patients had adult types of tuberculosis and were classified in regard to the extent of the lesion according to the "Diagnostic Standards" (1931) of the National Tuberculosis Association. In this system the Roman numeral "I" is used for minimal, "II" for moderately advanced, and "III" for far advanced lesions. In addition at Herman Kiefer Hospital, the character of the lesion is graded according to the tissue reaction (fibrinoid or nodular as opposed to pneumonic or infiltrative) by the letters "A," "B," and "C." The main significance of this is found in the fact that the prognosis for a relatively inactive "A" is much better than that for a progressive "C" lesion of the same degree of involvement, with that for "B" lying between. In Table I the cases in the group with collapse therapy and in the two groups without collapse therapy are shown according to this classification.

From Table I it can be seen that patients with far advanced tuberculosis (III) made up a slightly larger proportion of the groups without collapse (45 and 39 per cent) than with collapse (35 per cent). Moderately advanced involvement (II) was much more frequent in the group with collapse therapy, while the more favorable minimal tuberculosis (I) appeared more frequently among the cases without collapse therapy. Those entered as not classified had arrested, quiescent, or very early though definite lesions. Naturally, the majority of these highly favorable cases fell into the series without collapse. With one possible exception then, the differences compensate for each other to quite a degree, and it would appear that the three groups with or without collapse were fairly comparable

TABLE I. EXTENT AND CHARACTER OF TUBERCULOSIS IN CASES WITH AND WITHOUT COLLAPSE THERAPY BEFORE DELIVERY

	WITH COLLAPSE THERAPY	WITHOUT COLLAPSE THERAPY. TREATED IN HOSPITAL BEFORE DELIVERY	WITHOUT COLLAPSE THERAPY. NOT TREATED IN HOSPITAL BEFORE DELIVERY
IIIA	0	0	1
IIIB	19	4	9
IIIC	0	1	7
IIA	0	1	1
IIB	24	0	10
IIC	0	0	0
IA	5	0	8
IB	5	4	4
IC	0	0	0
Not classified	1	1	4
Totals	54	11	44

in regard to extent and character of the pulmonary conditions. The possible exception is found in the fact that all of the most serious cases (IIIC) were in the groups without collapse treatment. This will be referred to later.

COMPARATIVE MATERNAL RESULTS

The gross mortalities for the three groups during a period of one year after delivery were: (1) Six in 54 cases with collapse therapy during pregnancy; (2) 1 in 11 with hospital treatment before delivery but without collapse; and (3) 16 in 44 with little or no prenatal hospital treatment. All deaths occurred after delivery, and were due to tuberculosis except possibly one in the first group. This woman had been sent home with her tuberculosis arrested but died just at the end of the year while under the care of a private physician who could not be traced.

As indicated previously, the 3 series are very similar in regard to tuberculosis prognosis, except for the 8 very grave cases (IIIC) found in the two groups without collapse. It might be argued that the tuberculosis in these cases was possibly of a favorable type originally and became unfavorable due to the influence of pregnancy. However, as this is not certain, and as their elimination makes for better comparison of results in the period after delivery, they are not included in Table II and subsequently in this particular section of the paper.

TABLE II. RESULTS IN THE FIRST YEAR AFTER DELIVERY FOR THREE SERIES OF TUBERCULOUS WOMEN

SERIES	ARRESTED	IMPROVED	WORSE OR UNIMPROVED	DEAD	TOTAL
With collapse therapy	6	38	4	6 (11%)	54
Without collapse therapy but with prenatal hospital treatment	2	7	0	1 (10%)	10
Without collapse therapy or prenatal hospital treatment	11	10	7	9 (24%)	37

Although the groups in Table II are not large enough for definite conclusions, the differences are sufficient to indicate the advantages of prenatal hospital treatment for tuberculosis, with and without collapse therapy. This is shown not only in the mortality rates for the year post partum, but also in the much higher incidences of arrested and improved tuberculosis following prenatal hospital treatment. Attention is again called to the fact that the above results cannot be attributed to differences in the tuberculosis since elimination of the very grave cases from those without collapse has given all groups nearly the same prognosis so far as the pulmonary conditions are concerned. Actually the advantage, if any, ensuing from this elimination of cases would be in favor of the series without collapse therapy. Apparently, then, pregnancy has a serious effect on untreated tuberculosis which cannot be compensated for by the very best treatment after delivery.

No such clear-cut conclusion regarding the advantage, or not, of prenatal collapse therapy can be drawn from a comparison of the two series receiving hospital care during pregnancy, since these groups do not present a true contrast in treatment. These patients were all hospitalized for a sufficient time to have permitted collapse therapy, and with only a few exceptions the procedure chosen in each case was that which was considered by the phthisiologists to be most suitable for the individual pulmonary condition. A striking exception is the one patient in the second group who died post partum after persistently refusing collapse therapy during pregnancy. One can only conjecture as to the outcome had she followed advice. However, the instance in no way detracts from our high opinion of the accuracy shown by our phthisiologists in the choice of appropriate treatment.

From the literature and also from the general statistics for tuberculosis at Herman Kiefer Hospital, it appears that the results obtained for the patients receiving hospital prenatal treatment approached those to be expected in a group of nonpregnant women with comparable types of tuberculosis. From this it might be thought that the problem of tuberculosis and pregnancy could be solved by the provision of modern treatment for the tuberculosis, which would include collapse therapy in most cases. Though recognizing this to be true in great part, we believe from a careful analysis of our data that, in at least a few instances, pregnancy may be a cause of irreparable damage and death in spite of the most ideal tuberculosis treatment. This point will be discussed later.

COMPARISON OF EFFECTS ON PREGNANCY AND THE CHILD

The patients with collapse therapy in pregnancy were remarkably free of the well-known difficulties and dangers associated with this type of treatment. Dyspnea never occurred to any troublesome degree, and pleural effusion with pneumothorax made necessary cessation or limitation of this type of collapse in only a few cases. Digestive disturbances were of no practical importance except for one in-

stance of excessive and intractable vomiting which required premature induction of labor. This may or may not have had some connection with unilateral phrenic nerve operation in pregnancy.

Premature labor occurred in all groups approximately twice as frequently as among the general run of obstetric patients at this hospital. In the series of 54 with collapse therapy, there were 11 premature labors; in the 11 with hospital prenatal treatment but without collapse therapy, there were 2; and among the 44 with little or no hospitalization before delivery, there were 14 premature labors. There is no indication from these figures that collapse therapy was a factor in causing premature interruption of pregnancy. On the other hand, since the usual causes (syphilis, toxemia of late pregnancy, etc.) played little part here, it does seem that pulmonary tuberculosis, in itself and irrespective of type of treatment, was to blame to some degree. Among the 11 premature labors in the first group, there was the one induction because of persistent vomiting, and another patient had placenta previa. The remaining 9, however, and all of those in the other groups had no demonstrable cause. Although it is generally conceded that there are always an appreciable number of premature labors which are not definitely explainable, the incidence in these tuberculous women was so far beyond ordinary expectations as to implicate tuberculosis as a cause. Naturally, there was a high mortality (37 per cent) among the premature babies, but none, including those who died and were subjected to post-mortem examination, showed any evidence of congenital tuberculosis.

Where the pregnancies did go to term, there was no evidence of any great effect on the babies from the pulmonary condition. All term babies lived and were discharged in good condition. The 43 born of mothers who had collapse therapy during pregnancy had an average birth weight of 7 pounds and 6½ ounces, with approximately 85 per cent weighing 6 pounds or over. Those in the group with prenatal hospital treatment but not collapse therapy, and those in the series with little or no treatment before delivery averaged somewhat smaller, 6 pounds 13 ounces, and 7 pounds one ounce, respectively. However, they also did well in general. None of these babies born of tuberculous mothers were put to breast.

ADDITIONAL DATA REGARDING PATIENTS WITH COLLAPSE THERAPY DURING PREGNANCY

In addition to the foregoing comparisons between the different groups, we found that a more detailed study of the series with prenatal collapse therapy yielded interesting information. In the first place, though the mortality rate for the group as a whole was quite good from the standpoint of usual expectation in tuberculosis, there were some individual patients who were apparently incompletely protected against the effects of pregnancy and suffered very serious results. For example, a patient after two years of treatment in the hospital was discharged with the tuberculosis arrested and became pregnant three

months later. Because of reactivation of the lesion, she was admitted to the hospital in the fifth month of the pregnancy, but in spite of artificial pneumothorax, there was rapid progression with death three and one-half months after delivery. Four others were admitted early in pregnancy when therapeutic abortion was considered but was discarded because of the seemingly favorable prognosis. The disease progressed somewhat during pregnancy and then rapidly in the puerperium with the result that two died in the first year, one within two years, and the fourth was still in a serious condition at the end of fifteen months. It is granted that such results are also seen in the nonpregnant, and consequently, it is not easy to say in a given case to what extent pregnancy is responsible for the tragedy. However, failure of treatment to control progression during pregnancy would seem to be so nearly a sign of the woman's doom as to justify therapeutic abortion, provided, of course, that the pregnancy was still in the early months. Actually, we believe this to be the very minimum to which indications for therapeutic abortion should be restricted, even where ideal treatment is available.

Type of Collapse Therapy.—As noted before, our study was confined to pneumothorax and phrenic nerve operations during pregnancy and did not include thoracoplasty. The kind of collapse therapy selected for each case was apparently determined according to its suitability for the type of tuberculosis and bore no relationship to the presence of pregnancy. Phrenic nerve operation was performed in 22, pneumothorax in 21, and both in 11. A review of these cases in regard to the effects of collapse therapy on pregnancy and labor and the production of dyspnea and other symptoms offers no reason for recommending one procedure rather than the other since serious complications were absent in all groups. The differences in mortality—phrenic operation, 1 (4.5 per cent); pneumothorax, 3 (14 per cent); and pneumothorax plus phrenic operation, 2 (18 per cent)—seemed to be related to the definitely larger proportion of the more serious cases in the last two groups rather than to the procedures employed. The majority of those in the third group were subjected to phrenic nerve operations as well as pneumothorax because of unsatisfactory results from the latter operation, for bilateral disease, or for the purpose of producing persistent collapse.

Type and Extent of the Tuberculosis.—As noted before, in the patients treated by collapse therapy, no serious ill effects of this treatment could be definitely demonstrated. This was true regardless of the type or extent of the tuberculous lesions. In other words, there seems to be no contraindication to collapse therapy because of pregnancy no matter how severe the pulmonary lesion may be.

Table III seems to indicate that no reliable prognosis as to outcome in pregnant patients treated with collapse therapy can be made from the type and extent of the lesion alone. Although 4 of the 19 patients with the most serious lesions (IIIB) were dead at the end of a year, 13 were actually arrested or improved. On the other hand 2 of the 5

TABLE III. THE RESULTS OF COLLAPSE THERAPY IN PREGNANCY ACCORDING TO THE TYPE OF TUBERCULOUS LESION. PATIENTS TREATED FOR ONE YEAR AFTER DELIVERY

TYPE	ARRESTED	IMPROVED	UNIMPROVED OR WORSE	DIED	TOTAL
IIIB	1	12	2	4	19
IIB	4	18	2	0	24
IA	0	5	0	0	5
IB	0	3	0	2	5
Unclassified	1	0	0	0	1
Total	6	38	4	6	54

patients with the presumably much more favorable IB involvement were dead by this time, while the intermediate type IIB had much better results than either of the other two. This disparity in results may be explainable on the basis of the small number of cases involved or perhaps is due to some unknown factor or factors. The important point is that with collapse therapy, and regardless of the kind of tuberculosis, 44 (81 per cent) of 54 cases were actually arrested or improved at the end of a year after delivery in spite of pregnancy and labor.

Time of Beginning Treatment.—The general impression gained from the literature is that the prognosis for patients in whom tuberculosis had been discovered and treated before the occurrence of pregnancy is better than in those who first become aware of their tuberculosis and begin treatment sometime during the course of pregnancy. The results in our 54 cases seem to confirm this belief, as illustrated in Table IV.

TABLE IV. RESULTS ONE YEAR POST PARTUM ACCORDING TO INSTITUTION OF HOSPITAL TREATMENT BEFORE OR DURING PREGNANCY

	ARRESTED	IMPROVED	UN-IMPROVED	DIED	TOTAL
Treatment begun before pregnancy	3 (16%)	14 (74%)	1 (5%)	1 (5%)	19
Treatment begun during pregnancy	3 (9%)	24 (68%)	3 (9%)	5 (14%)	35

When treatment (with or without collapse therapy) was started before pregnancy, 90 per cent of the patients showed arrested or improved pulmonary lesions one year after delivery, as opposed to 77 per cent when treatment was first begun during pregnancy. Careful examination of our material showed no good reason for this difference, except the duration of treatment, and consequently we can neither confirm nor deny any of the other explanations found in the literature.

It should also be noted that where institution of early collapse was a part of the treatment, results at the end of a year were especially good. Of the 18 patients so treated before pregnancy (2) or in the first trimester of pregnancy (16), only one died and the remaining 17 (94 per cent) were either arrested or improved.

There is a common belief that collapse therapy should not be begun late in pregnancy because of the probability of respiratory and other

difficulties. The results in our series indicate the direct opposite, since among the 20 cases with such treatment instituted in the last trimester there were none with serious trouble or discomfort. Phrenic nerve operations were done in 11, pneumothorax in 9, and both operations in one instance for bilateral tuberculosis. Actually, pneumothorax collapse was begun in four patients and phrenic nerve operation was done in one case as late as the last month of pregnancy without important disturbance.

Race.—Although it is generally conceded that negroes as a race show less resistance to tuberculosis than do whites, there is little or no discussion of this in regard to pregnancy and tuberculosis. We have failed to find a single report of a negress who received collapse therapy during pregnancy, though there no doubt have been such cases in this country. Among our 54 tuberculous women with collapse therapy during pregnancy, there were 10 negresses. The distribution of the two races in regard to type of lesions, time of treatment, etc., was approximately the same, and yet the results were strikingly different, as shown in Table V.

TABLE V. RESULTS ONE YEAR POST PARTUM FOR NEGRO AND WHITE WOMEN TREATED BY COLLAPSE THERAPY DURING PREGNANCY

	ARRESTED	IMPROVED	UNIMPROVED OR WORSE	DIED	TOTAL
Negro	1	5	1	3 (30%)	10
White	5	33	3	3 (7 %)	44

Table V indicates that tuberculous negresses who bear children may do badly in spite of collapse therapy. Such an outcome might be expected, but its actual demonstration is clinically important. Moreover, the statistical aspects of this observation are also of no little importance when it is seen that less than one-fifth of the group accounts for one-half of the mortality. Certainly, the point should be taken into account whenever results from different clinics are compared.

Parity.—It has been stated with various explanations, that tuberculous women who are pregnant for the first time generally fare better than those who have previously borne children. Our group of 54 patients with collapse therapy included 18 primigravidas and 36 women who had been delivered of one or more term or premature children. Results for these are tabulated in Table VI.

TABLE VI. RESULTS ONE YEAR POST PARTUM FOR TUBERCULOUS PRIMIGRAVIDAS AND MULTIGRAVIDAS TREATED WITH COLLAPSE THERAPY DURING PREGNANCY

	ARRESTED	IMPROVED	UNIMPROVED OR WORSE	DEAD	TOTAL
Para i	5	9	1	3 (17%)	18
Para ii plus	1	29	3	3 (8%)	36

Table VI shows a higher mortality for primigravidas. On the other hand the proportion of those who were improved or arrested at the end

of a year was approximately the same, 14, or 78 per cent, for the primigravidas and 30, or 83 per cent, for multigravidas. Correction for race made no essential difference in the results. However, the relatively larger number of the most serious cases among the primigravidas was important. In any event, it is evident that the smallness of both series precludes definite conclusions.

Bilateral Tuberculosis and Bilateral Collapse Therapy.—A comparison of results for patients with unilateral tuberculosis and for those with bilateral involvement is shown in Table VII.

TABLE VII. RESULTS ONE YEAR AFTER DELIVERY FOR PATIENTS WITH UNILATERAL AND WITH BILATERAL TUBERCULOSIS, TREATED BY COLLAPSE THERAPY DURING PREGNANCY

	ARRESTED	IMPROVED	UNIMPROVED OR WORSE	DEAD	TOTAL
Unilateral tuberculosis	1	18	1	2 (9.0%)	22
Bilateral tuberculosis	5	20	3	4 (12.5%)	32

It is not unexpected that women with bilateral tuberculosis who go through the strain of pregnancy and labor should have a higher mortality at the end of a year than those with only one side affected. The surprising thing is that the difference is no greater than that shown in Table VII. The more so when it was found that 16, or 50 per cent, of those with bilateral disease were classified, on the findings in the more affected side, as having the serious IIIB involvement as compared to only 3, or 13 per cent, of those in the group with only one lung involved. In other words, 32 women with bilateral tuberculosis, of whom one-half had far-advanced lesions in the more involved side, were carried through pregnancy and labor with 25 (78 per cent) arrested or improved and only 4 (12.5 per cent) dead at the end of a year following delivery. Such results speak highly for collapse therapy.

In reviewing the literature, we have found only a few case reports where the apparently radical procedure of bilateral collapse was performed. Four of our most seriously ill patients with bilateral disease were subjected to this treatment. Bilateral pneumothorax was performed on two patients, and on the other two artificial pneumothorax was done on one side, and phrenic nerve operation on the other. All patients were remarkably free of symptoms though two went into labor somewhat prematurely. All babies survived. One of the mothers died four months after delivery, while another was somewhat improved at the end of a year. A third was made worse and was still in a precarious condition fifteen months later. The fourth failed to improve and finally died on the third day after a thoracoplasty operation. Poor results in these cases were apparently due to the severity of the tuberculosis. The important point is that bilateral collapse therapy seems to be practicable in pregnancy.

Anesthesia.—Many of our patients were delivered without anesthesia, especially in the earlier years. More recently, there was an increasing and satisfactory employment of analgesic drugs, with resort to spinal

or local infiltration anesthesia in operative deliveries. For some reason, ether anesthesia was unfortunately given in five of the early cases, and it is worthy of note that two of these patients died later. We are in accord with the accepted opinion that ether is contraindicated in pulmonary tuberculosis.

Results After Two Years.—As stated before, we considered the first year following delivery as sufficient time to show the effects of pregnancy and labor on the patients with collapse therapy. However, results from at least one carefully studied series (that of Rist and Jottras) were calculated for two years. In our series, if we eliminated the 12 for 1936, there were 42 patients who were delivered at least two years before Jan. 1, 1938. It was possible to definitely trace 29 of these for two years or more, and the results are shown in Table VIII.

TABLE VIII. RESULTS TWO YEARS OR MORE AFTER DELIVERY FOR TUBERCULOUS PATIENTS RECEIVING COLLAPSE THERAPY DURING PREGNANCY

ARRESTED	IMPROVED	UNIMPROVED OR WORSE	DEAD	TOTAL
10	10	1	8 (28%)	29

Of the remaining 13 patients, 6 were discharged from the hospital as arrested. Five others were considered sufficiently improved to be released for care in the outpatient clinic, but failed to report or else disappeared from there later. The remaining two were greatly improved when discharged, one being sent to another hospital and the other to her private physician. If we should arbitrarily assume that the arrested cases were well at the end of the two-year period (which is probable), and that all seven classified as "improved" either died later or became worse (which is unlikely), there would be 26, or 62 per cent, with good results at least two years after delivery. Such results are definitely better than those in the series reported by Rist and Jottras. In fact, our figure compares well with that obtained in their most favorable group, composed of the patients with collapse therapy begun before pregnancy. Incidentally, we believe that this is the only approach to a fair comparison which can be made between our results and those reported in the literature because of differences or uncertainties regarding the length of observation periods and because of such varying factors as therapeutic abortion, type of tuberculosis, and race.

SUMMARY AND CONCLUSIONS

Opinion regarding collapse therapy in pregnant tuberculous women is generally favorable. That collapse therapy represents a great advance in treatment seems certain. However, a review of the few sizable series of cases, all reported in the foreign literature, fails to show such uniformly good results as to justify the belief that a complete solution of the problem of tuberculosis and pregnancy has as yet been found. Certainly, as a guide in treatment of the individual patient, there are much essential data and desirable information still lacking.

Our study concerns the results for one year after delivery in 109 tuberculous women who were adequately treated post partum for their tuberculosis. One group of patients received little or no treatment during pregnancy; while the remainder were in the hospital for two months or more before delivery, and in the majority of cases received collapse therapy in the form of artificial pneumothorax, phrenic nerve operation, or both. The mortality for those without prenatal treatment was much higher, and this was the case even after ample allowance was made for differences in extent and type of the pulmonary lesions. Premature labor had a high incidence, and as this was true in all groups regardless of kind of treatment, it would seem that the tuberculosis itself was a causal factor. Babies born at term survived and did satisfactorily in all groups.

A detailed study of the 54 cases with collapse therapy yielded interesting information. Although results for the series were generally good, there were at least five patients who would probably have fared better if early therapeutic abortion had been done. The choice of the type of collapse therapy was seemingly made on the basis of its suitability for the particular pulmonary lesion and with little or no consideration for the presence of pregnancy. Collapse therapy caused no serious ill effects regardless of the type and extent of the lesions. Apparently with collapse therapy, no reliable prediction as to the outcome can be based on the seriousness of the tuberculosis. Actually, a majority of even our worst cases did well. Results in our series were especially good when there had been treatment for the tuberculosis before pregnancy and also where collapse therapy was instituted not later than the first trimester of pregnancy. There were no serious symptoms from collapse therapy, even when this was begun in the last trimester, or, as in five instances, during the last month of pregnancy. Negresses had a high mortality in spite of collapse therapy. Women who had previously borne children fared better than primigravidas, though this could have been due to the fact that the latter group included an undue proportion of the most serious cases. The same explanation is possible for the slight advantage of unilateral over bilateral involvement. Bilateral collapse was well tolerated in four very ill patients. Many patients were delivered without anesthesia until later years when satisfactory use was made of analgesic drugs for spontaneous, and spinal or local anesthesia for operative delivery. Two of the five patients given ether died before the end of the year. Results for patients who were followed two years or more after delivery compared well with those for a fairly comparable series reported by Rist and Jottras.

We desire to express our appreciation to the Members of the Divisions of Tuberculosis and Thoracic Surgery of Herman Kiefer Hospital for their aid in the preparation of this report.

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A STUDY OF SUSPENDED HUMAN UTERINE MUSCLE STRIPS IN VITRO*

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INTRODUCTION

THE various methods used for studying the physiology of human uterine muscle have features which limit their practical application. The intrauterine hydrostatic bag[1] valuable in studying the post-partum uterus[2] cannot be used safely during pregnancy or parturition and does not give the reaction of the upper uterine segment as it lies in the lower segment. Recently work has been done using this method in the nongravid uterus.[3] Even the small degree of artificial cervical dilatation necessary for the introduction of the bag alters the normal motility of the muscle and to some degree vitiates the observations made when medicaments are administered.

Artificial uterine fistulas[4] used advantageously in animal experiments are obviously impractical in studies on the human being.

The glass window for direct visualization of the organ and the operation for exteriorizing the uterus are methods applicable to investigations in animals but not in the human being.

The Dodek[5] apparatus for measuring and graphically recording abdominal wall displacement by changes in size and shape of abdominal viscera has helped in analyzing uterine activity. An exterior method of approach has been devised by Fenning and Bonar who used an electrical oscillocapacigraph.[6] This method has great promise as a sensitive means of recording these displacements due to uterine contractions. Here again the procedure is limited in that it is applicable only after the third month of pregnancy and for the first few days of the puerperium and cannot be used for studies of the nonpregnant uterus.

All of the methods applicable to experiments on the human uterus in vivo have the following disadvantage, namely, that the uterus is

*Presented at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938. This paper was awarded the annual prize for the best investigative work submitted during the year 1938.

constantly under the influence of the many complex hormonal secretions. Consequently, one has to bear in mind that the environmental and emotional stimuli which are present may have a profound effect on the results.

The present method of study has been used extensively in animals but only to a limited extent in the human. Guinea pig uterine cornu[7] suspended in vitro is the method by which many of our standard biologic agents are assayed. Uterine tissue excised from the rabbit,[7] cat, dog, and monkey have all been used extensively.

Technical difficulty in carrying out the study of human uterine strips is one of the many reasons why the method has not been more popular.

This study was undertaken with the desire to observe the direct effect of five commonly used drugs without the influence of the elements present in the blood stream and with the hope that this method might help to clarify our conception of the action of these drugs on human uterine muscle.

HISTORICAL SKETCH

E. Kehrer[8] in 1907 first published studies on the excised human uterus. He described the natural contractions which regularly occur. Flury[9] also published observations on this phenomenon in 13 different excised human uteri. Before the work of Sun[10] little had been written regarding studies in vitro on the normal human uterus. He published a comprehensive report on certain "definite and constant phenomena which were observed in 57 isolated human pregnant uteri, studied in the laboratory of the Woman's Clinic of the Johns Hopkins Hospital." This contribution followed a similar but less comprehensive report by Keye.[11] Kamm[12] fractionated the posterior pituitary extract into a vasopressor and oxytocic principle and gave impetus to further investigations. Recently Miller, Cockrill, and Kurzrok[13] reported studies on excised nongravid human uteri and their reactivity to pituitrin, acetylcholine and adrenalin.

Robson[14] studied the reactivity and activity of the human uterus at various stages of pregnancy and at parturition (in vitro). He found an absence of reactivity to both oxytocin and vasopressin during the earliest stages of pregnancy. This was followed by a period of greater reactivity to vasopressin than to oxytocin, and last, a gradual increase in reactivity to oxytocin culminating in labor.

Much has been written regarding the changes in activity and reactivity of the uterine muscle after the rupture of the Graafian follicle and the formation of the corpus luteum. Knaus[15] claims that the uterine muscle ceases its natural rhythmic activity and loses its response to stimulation by posterior pituitary extracts. Falls, Lackner, and Krohn,[16] and others have been able to inhibit a pituitary response in vivo by previous administration of progestin in studies on the human being.

Makepeace, Corner, and Allen[17] were able to produce inhibition of pituitrin response and inhibition of estrus motility in the rabbit uterus by production of pregestational proliferation following injections of progestin. Illingworth and Robson[18] showed the same thing in 75 per cent of their cases in studies on ovariectomized rabbits.

MATERIAL

All specimens for study were obtained at operation in the Chicago Lying-in Hospital. One hundred strips were studied and their activities recorded. Sixty of these were from nongravid uteri, which were

removed for a variety of conditions, mostly for myomas. Many uteri were not pathologic but were removed by vaginal hysterectomy because of varying degrees of uterine prolapse.

Forty strips were from gravid uteri. Included in this group are eight strips obtained at abdominal hysterotomy done for purposes of termination of early pregnancy and of sterilization. The remaining thirty-two were removed from the uterine incisional edge at cesarean section.

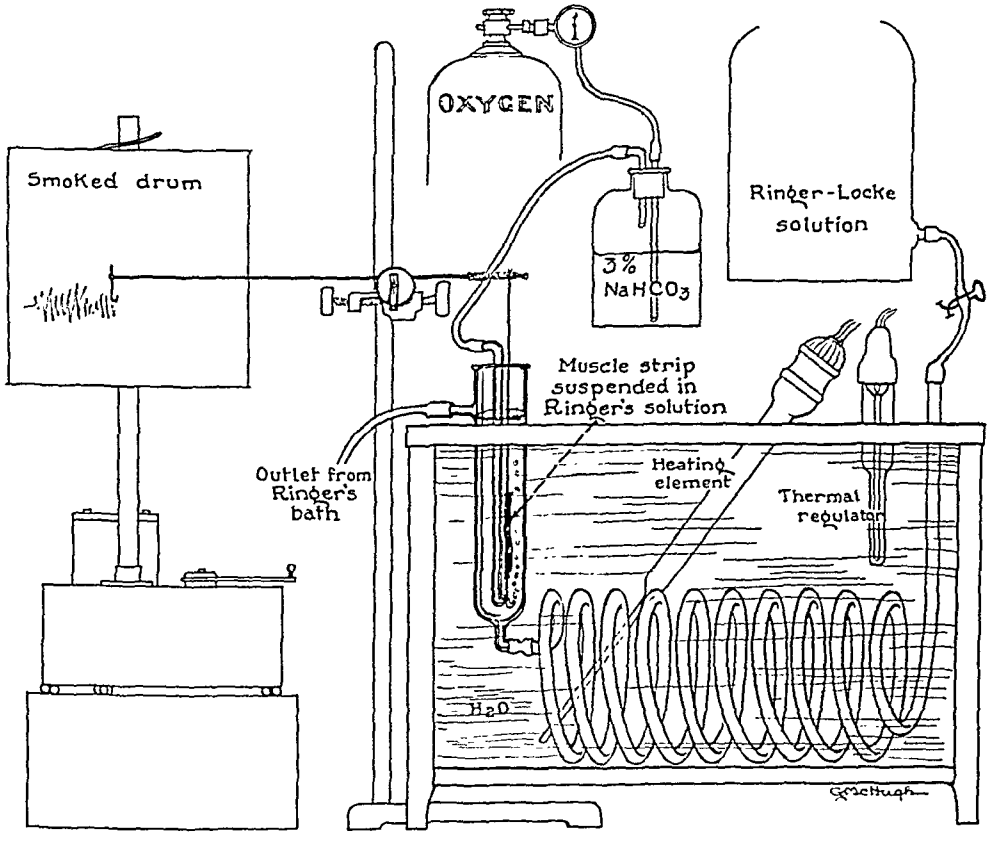


Fig. 1.—Apparatus.

METHOD

The muscle strip intended for study either was suspended immediately in the apparatus to be described or was placed in Ringer-Locke solution in the ice box, thus preserving its vitality for many hours or even days without apparent effect on its normal activity or response to drugs. The mucosa of the nongravid uteri were studied microscopically to determine whether they were in the proliferative or secretory phase of the menstrual cycle.

The apparatus (Fig. 1) consisted of a large glass tank filled with water and equipped with a heating element and an automatic thermal regulator which kept the water at a constant temperature of 37.5° C. Circulation was maintained in the tank and an even temperature was insured at all levels by means of a stream of compressed air bubbling through.

A glass tube holding 100 c.c. of the Ringer-Locke solution was immersed in this water. In the tube two muscle strips were suspended, their lower ends being fixed and their upper ends being attached by a silk thread to a lever which recorded the contractions and relaxations on a kymograph drum. A fine stream of oxygen,

which had previously passed through a 3 per cent sodium bicarbonate solution, bubbled continuously through this Ringer bath.

The inlet to this Ringer bath was at its lower end and the outlet at the top. The inlet was connected to a series of coils through which the solution would run before entering the bath. Thus the strips could be rapidly washed with new solution without danger of temperature change. The Ringer-Locke solution was freshly made each day to insure as little change as possible in pH value. Van Dyke and Hastings[19] showed conclusively that changes in ionic concentration alter the activity and reactivity of muscle suspended in vitro.

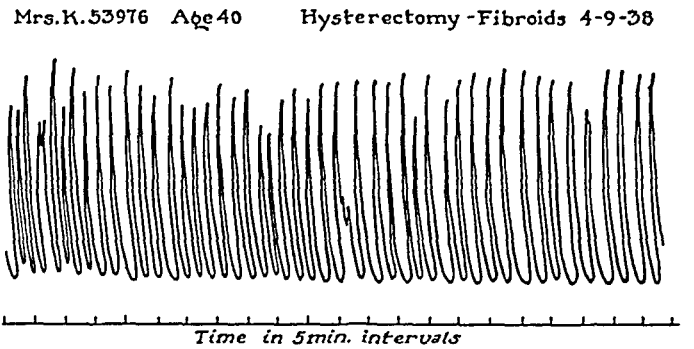


Fig. 2.—Showing natural contractions occurring in the strip. This tracing starts approximately three hours after the strip was suspended in the apparatus.

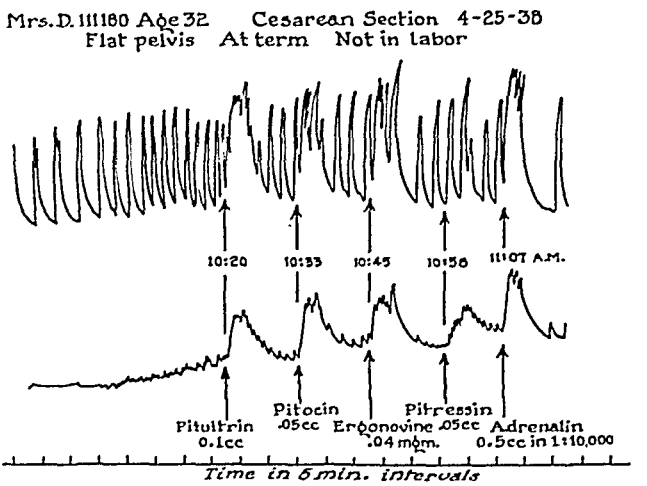


Fig. 3.—Showing tracings of two strips from the same uterus set up simultaneously in the apparatus. Although there was a difference in amplitude and speed of natural contractions the response to drugs was the same.

The strips were allowed to contract and relax naturally for an hour or more before any medication was added to the bath (Fig. 2). Each would exhibit its rhythm independently. Often parallel strips from the same area in the same uterus would show different amplitude and speed of contractions. However, the presence or absence of response to drugs was nearly always the same in strips from various areas of the same uterus (Fig. 3).

Frequent washing with fresh Ringer-Locke solution had little, if any, effect on the rhythmicity. There was no more change than would often occur naturally without change of solution.

The various drugs were added directly to the bath by means of a pipette. After two minutes the solution was changed, 300 c.c. being allowed to run through the bath to insure complete removal of all the medicament. The muscle strips would then

resume their original activity. Ten minutes to several hours were allowed to elapse between instillations of drugs.

Dosage.—It was found that 0.1 c.c. (one unit) of pituitrin, pitressin, and pitocin added to the bath would initiate a satisfactory response if the muscle were not refractory to the drug. In every case where this amount failed, larger doses also failed. In some of the earlier experiments larger doses were used. Ergonovine was used in doses of 0.05 mg. to 0.1 mg. Adrenalin was used in very small doses, 0.5 c.c. of a 1:10,000 solution being sufficient.

Interpretation of Graphs.—In nearly all cases the response or lack of response to a drug was a very definite thing. When the strip was sensitive to the drug the lever rose promptly much higher than during the natural rhythmic activity. The muscle would remain in this tetanically contracted state until all the drug was

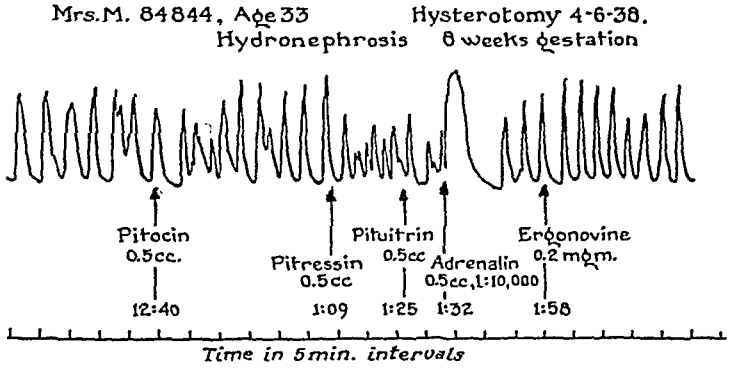


Fig. 4.—Showing tracings from a muscle strip removed at hysterotomy done for termination of pregnancy and for sterilization. Except for adrenalin, there was no response to the medicaments.

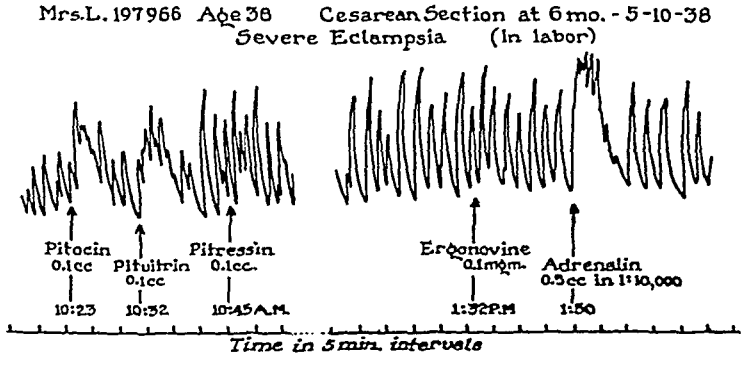


Fig. 5.—Showing tracings of a strip removed at cesarean section done at the end of the second trimester of pregnancy. Here a response to pituitrin, pitressin, pitocin, and adrenalin can be seen. This case was in beginning labor before operation was begun.

washed out by flushing fresh Ringer solution through the bath. In a few instances the ascent of the lever would be no higher than for the unstimulated contractions but would remain at the level until the strip was washed (Fig. 5). If the drug caused this tetany it was interpreted as a positive result. Nearly all positive responses could be repeated many times. In a very few instances there was no repetition of the response. However, if the response was definite in one instance the result was considered positive. The sequence of instillation of the medicaments was frequently changed because of the chance that one oxytocic might affect the reactivity of the muscle to the others.

Results.—There was a marked variation in the sensitivity of uterine muscle to the drugs. Adrenalin caused a prompt tetanic contraction in nearly every case, but there was no such consistency with the other four medicaments. The response of the strips from uteri of early pregnancy (Fig. 4) was entirely different from that of strips obtained at term or in labor. Two of the strips were removed at cesarean

section done about the twenty-sixth week of gestation. Before the section was done there was a small amount of cervical dilatation after a few hours of weak labor pains. These two strips showed the same sensitivity that was manifested in uteri at term and in labor; namely, a prompt tetanic contraction after the addition of oxytocics (Fig. 5).

The strips from nongravid uteri showed some difference in response depending on whether the organ was in the proliferative or secretory phase of the menstrual cycle.

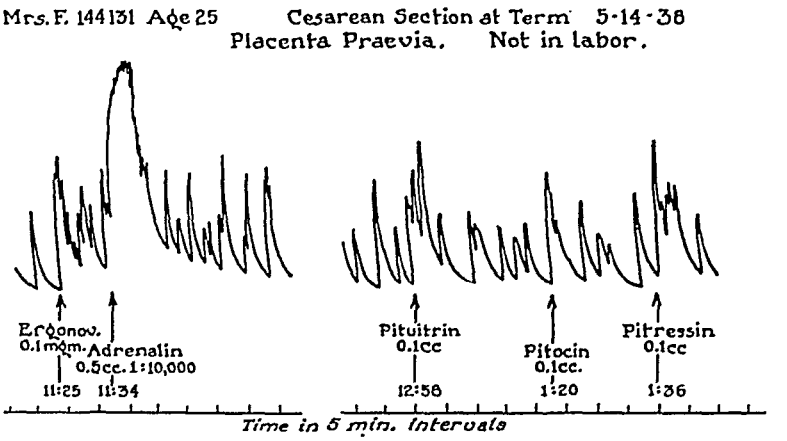


Fig. 6.—Showing that a strip from a gravid uterus at term is sensitive to oxytocics added to the Ringer bath.

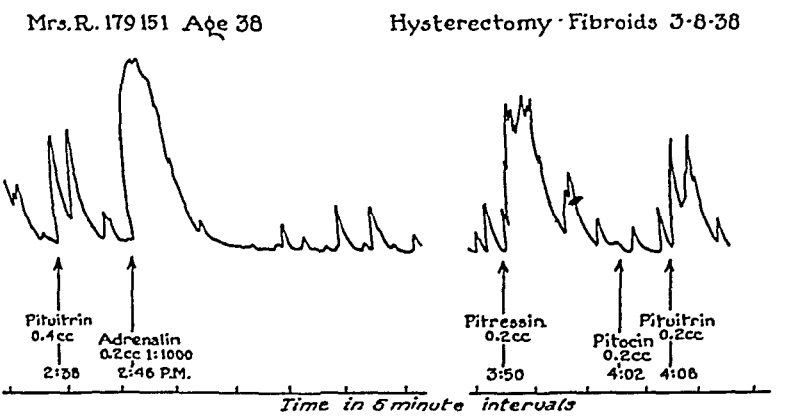


Fig. 7.—Showing the tracing from a strip taken from a uterus removed for myomas. The endometrium from this uterus was in the proliferative phase.

Pituitrin initiated a definite response in all strips from gravid uteri that were in labor and in strips from gravid uteri at term but not in labor (Fig. 6). Of the 8 strips from pregnant uteri not at term or in labor, no response whatsoever could be elicited (Fig. 4), and no change in rate or amplitude of the natural rhythmic contractions could be detected.

Of the strips from nongravid uteri in the proliferative phase 16 out of 36, or 44.4 per cent, responded to pituitrin stimulation (Fig. 7). Of the 24 in the secretory phase, only 5, or 20.9 per cent, responded (Fig. 8).

Pitressin also caused a response in all strips from uteri in labor and from uteri at term but not in labor (Fig. 9). The 8 strips from uteri early in pregnancy failed in every instance to show any effect from pitressin stimulation (Fig. 4).

Of the 59 strips, from nongravid uteri in the proliferative phase to which pitressin was added, 15 out of 35, or 42.9 per cent, responded. Of the 24 in the secretory phase, 8, or 33.3 per cent, responded.

Pitocin gave a lower percentage of response under all conditions than did either pituitrin or pitressin. Eight of the 9 strips from cases in labor responded, or 88.9 per cent. Of the 21 strips from uteri at term but not in labor, 19 or 90.5 per cent, responded to pitocin stimulation.

Of the 55 strips from nongravid uteri to which pitocin was added only 3 out of 31, or 9.7 per cent, of those in the proliferative phase responded. Of the 24 strips in the secretory phase, none showed the slightest response.

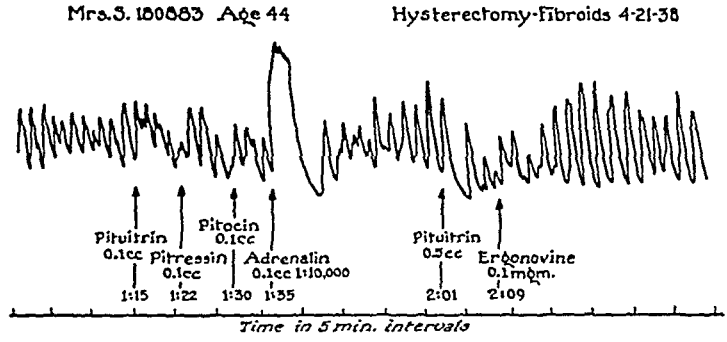


Fig. 8.—Showing a lack of response in every instance except on addition of adrenalin. The endometrium from this uterus was in the secretory phase.

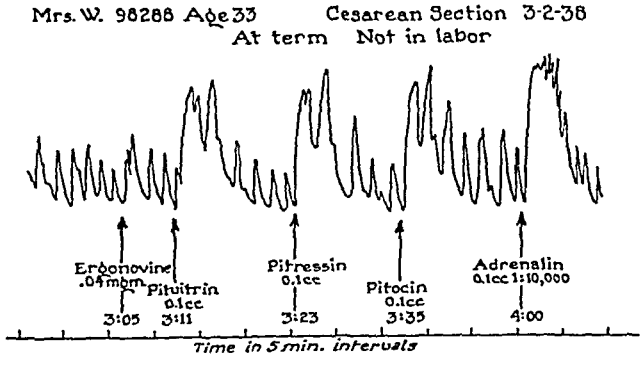


Fig. 9.—This tracing shows again the irritability of the muscle strip when the uterus was at term before the cesarean section was done.

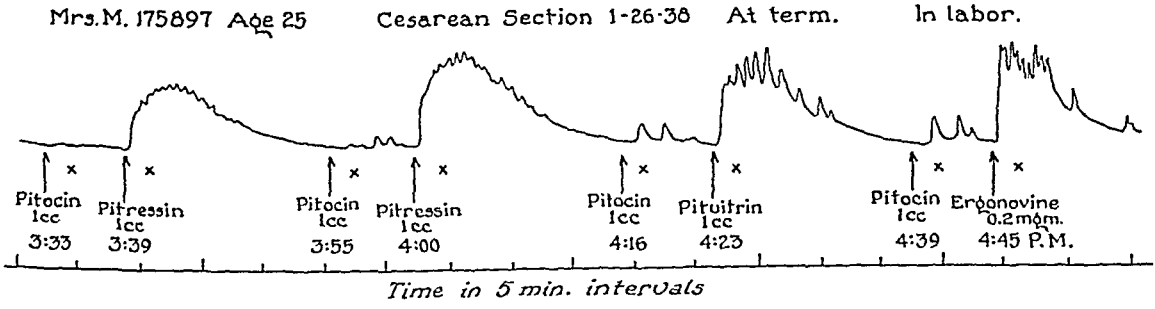


Fig. 10.—Showing a comparison between pituitrin, pitressin, pitocin, and ergonovine. In four attempts we were unable to get a response from pitocin. The *X* shows when the medicament was washed out of the Ringer bath.

Ergonovine failed to initiate any response in 6 strips from gravid uteri in early pregnancy. Of those from uteri in labor, 3 out of 9 responded, or 33.3 per cent. Of the 23 strips from uteri at term but not in labor, 11, or 47.8 per cent, responded.

Here again in the nongravid uteri there was a marked difference in the response depending on the phase of the menstrual cycle. Six out of 29, or 20.7 per cent, of those strips from uteri in the proliferative phase responded to ergonovine stimulation, whereas none of the 18 from the secretory phase did.

Adrenalin unquestionably gave the highest percentage of responses. Incidentally, in no instance was there a relaxation or even a diminution in amplitude of natural contractions following its addition to the Ringer bath. On the contrary, only two muscle strips failed to respond with marked tetanic contractions. These strips were from gravid uteri at term but not in labor prior to the hysterotomy.

All of the remaining 78 strips, including those from both gravid and nongravid uteri, gave a very positive response.

COMMENT

The entire experiment was done on a qualitative basis and in no instance was an attempt made to study the quantitative action of the medicaments. After a satisfactory minimum dose was determined

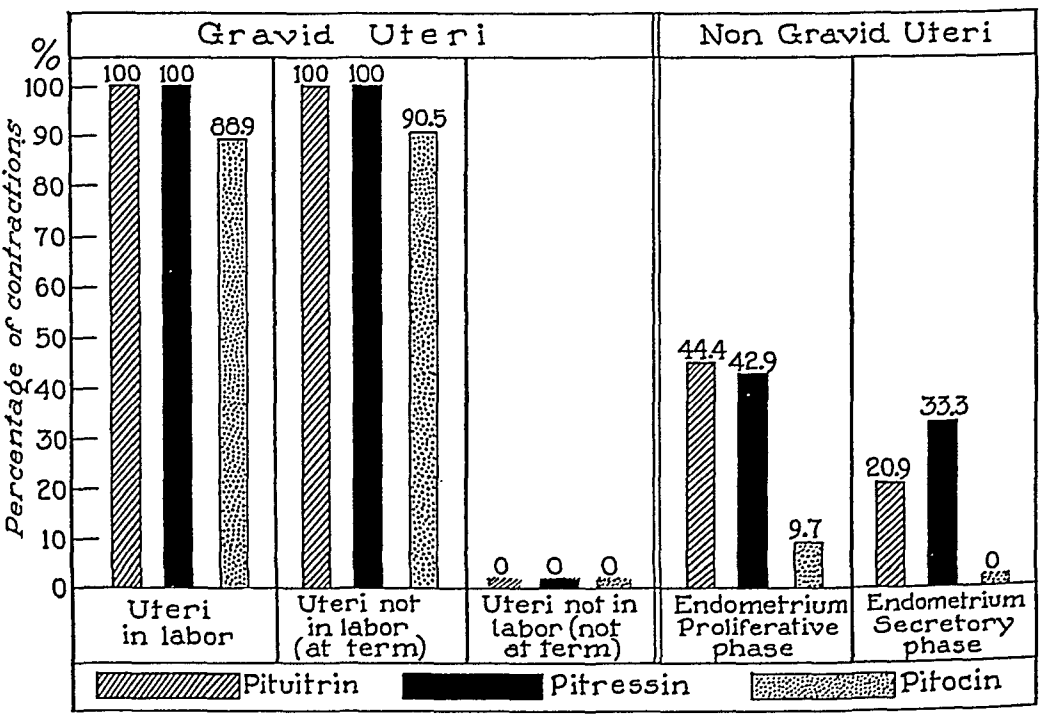


Fig. 11.

MUSCLE STRIPS FROM GRAVID UTERI (40)

	PITUITRIN	PITRESSIN	PITOCIN	ERGONOVINE	ADRENALIN
Uteri in labor (9)	9+* 0-†100%	8+ 0- 100%	8+ 1- 88.9%	3+ 6- 33.3%	6+ 0- 100%
Uteri not in labor At term (23)	23+ 0- 100%	21+ 0- 100%	19+ 2- 90.5%	11+ 12- 47.8%	14+ 2- 87.5%
Not at term Not in labor (8)	0+ 8- 0%	0+ 8- 0%	0+ 8- 0%	0+ 6- 0%	8+ 0- 100%

MUSCLE STRIPS FROM NONGRAVID UTERI

Endometrium in proliferative phase (36)	16+ 20- 44.4%	15+ 20- 42.9%	3+ 28- 9.7%	6+ 23- 20.7%	28+ 0- 100%
Endometrium in secretory phase (24)	5+ 19- 20.9%	8+ 16- 33.3%	0+ 24- 0%	0+ 18- 0%	22+ 0- 100%

*+ contraction.
†- no contraction.

that dose was maintained throughout. The same dose of pituitrin, pitressin, and pitocin was maintained on each single strip thus allowing comparisons of their efficacy.

Ergonovine gave a very small percentage of responses. We were unable to find any report of human uterine (in vitro) experiments where ergonovine was used. Robson[14] in 1933 used this method of study for ergotoxin and found, as we did, a lack of response except in gravid uteri at term. Unfortunately no post-partum uteri were available for study. During this phase ergonovine has been proved efficacious clinically and by studies with the hydrostatic intrauterine bag.[2]

The action of adrenalin was most interesting. Contrary to clinical studies reported by Rucker,[20] Urner,[21] McKenzie,[22] and others it invariably caused a prompt and strong contraction. Gunn and Gunn[23] concluded that the action of adrenalin corresponds to stimulation of a sympathetic nerve. It may be a motor to some organs and an inhibitor to others. They claimed that uterine contractions are inhibited by adrenalin only in the rat and guinea pig. This is true whether the uterus is gravid or nongravid, whether isolated or in situ. In other animals they feel the action of adrenalin is stimulatory.

The comparisons between pituitrin, pitressin, and pitocin are worthy of comment. Pitocin, which, according to Kamm,[12] is a 90 per cent pure oxytocic fraction, gave under all conditions a much lower percentage of responses than did pitressin which is the vasopressor fraction of the posterior lobe extract. Pituitrin and pitressin seem almost equal in ability to stimulate a contraction. In many instances, however, the amplitude of the curve was much greater with pitressin than with pituitrin (Fig. 7). It is of interest that in no instance did pitocin cause a contraction where pitressin failed to do so. However, in many instances pitressin initiated a response where pitocin failed (Fig. 10). In a few instances pitressin was successful where even pituitrin failed.

As previously stated, we classified our strips from nongravid uteri according to the phase of the menstrual cycle indicated by the endometrium. The results suggest a definite correlation between the phase and the susceptibility to posterior pituitary extracts.

SUMMARY AND CONCLUSIONS

1. One hundred muscle strips, 40 from gravid and 60 from nongravid uteri, were studied in vitro and their activities and reactivities graphically recorded.

2. Ergonovine excited a response in few cases other than those at term and in labor though there was no opportunity to observe its action on strips derived from post-partum uteri.

3. Adrenalin caused a prompt contraction in nearly every strip both in the gravid and nongravid uteri.

4. Pituitrin, pitressin, and pitocin caused a contraction in strips from gravid uteri at or near term.

5. Early in pregnancy the uterine strips were insensitive to posterior pituitary extracts except in one case where labor had begun before excision of the strips.

6. Pitressin under all phases of both gravid and nongravid uteri seemed to excite a higher percentage of contractions than did pitocin when muscle strips were studied in vitro.

7. In the nongravid uteri a correlation between the phase of the menstrual cycle and sensitivity to posterior pituitary extracts is suggested.

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DO ECLAMPSIA AND PRE-ECLAMPSIA CAUSE PERMANENT VASCULAR RENAL PATHOLOGY?*

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IT IS of the greatest importance to the physician to be able to recognize the various types of toxemias of pregnancy. The management of the pregnancy, the possibility of obtaining a living baby (which may be the only child), and the advisability of future pregnancies depend on whether or not the disease process will cause permanent vascular or renal pathology.

No textbook states specifically what percentage of eclamptic or preeclamptic patients are likely to have permanent vascular renal damage, a recurrence of the toxemia, a subsequent normal pregnancy, or what percentage are likely to abort, have an abruptio placentae, a stillborn fetus, etc. Answers to these various questions may be found in certain of the articles which have been published. We have evaluated these

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

various reports, as well as our own data obtained from repeat pregnancies after toxemia, and have arrived at tentative answers to the above questions.

The obstetric textbooks of a few years ago stated that eclampsia and pre-eclampsia do not recur and that if a patient has a repetition of the toxemia, it is because she has a chronic nephritis. The incorrect use of the latter term has been the stumbling block which has materially retarded a proper understanding of the toxemias of pregnancy for at least a decade. If hypertension and/or albuminuria are found at six months or more post partum, the condition is termed "chronic nephritis" by many obstetricians. These patients would be classified by us as having essential hypertension or vascular renal disease, with the latter term used only where there is evidence of some renal involvement. The term "chronic nephritis" is restricted to those patients who have previously had an acute glomerulonephritis.

A great part of the uncertainty about the toxemias of pregnancy is due to the numerous classifications used. For five years we have been dividing our cases into eclampsia, pre-eclampsia, essential hypertension, vascular renal disease, and acute or chronic glomerulonephritis. Definite criteria for each group have been given in a previous paper. We have been able to demonstrate that there are distinct differences between these various groups with regard to age and parity of patient, time of onset of the toxemia, height of blood pressure, presence or absence of edema and proteinuria, fetal weight, fetal mortality, etc. For example, we found that 74 per cent of the pre-eclamptic patients were 13 to 29 years old and 66 per cent were primiparas, as compared with the vascular renal group in which 34 per cent were 13 to 29 years old and only 11 per cent primiparas. The fetal mortality of the severe pre-eclamptic group was 10 per cent and of the severe vascular renal group 32 per cent. The present paper emphasizes differences in subsequent pregnancies.

Over 115 papers dealing with the follow-up of patients who have had toxemia of pregnancy have been studied. The data given in Tables I and II were selected from those articles which had the largest number of patients adequately studied. We picked especially reports of cases in which a subsequent pregnancy had occurred after toxemia because it is generally agreed that pregnancy is the best test of the vascular renal system.

We have listed the number of years the follow-up covered. It is incorrect, we believe, to examine patients ten or more years after delivery and ascribe their hypertension, albuminuria, retinal changes, or renal impairment to the previous pregnancy.

Thus, Herrick and Tillman followed one patient through 8 pregnancies from 1918 to 1933. After the fifth, in 1925, she had hypertension and albuminuria for a time but the seventh pregnancy in 1928 was normal. The patient died in 1933, aged 42 years, of uremia and cardiac failure. The autopsy revealed generalized arterio- and arteriolosclerosis. Because the patient had a mild toxemia with the first pregnancy, they ascribed all subsequent vascular renal disease to this toxemia of pregnancy. Peters also followed some of his patients for twenty years and attributed in some cases the pathology found at autopsy to a toxemia of pregnancy which occurred ten or more years previously. Peters states that "toxemias of all kinds

TABLE I. CONVULSIVE TOXEMIA—ECLAMPSIA

	YEAR	NUMBER CASES	HISTORY TOXEMIA %	YEARS FOLLOW-UP	CHRONIC NEPH. %	HYPER-TENSION %	HYPER. AND/OR ALBUM. %	RECURRENCE OF		NORMAL DELIVERY %
								ECL. %	TOXEMIA %	
Baisch	1913	60					10			
Slemons	1913	20							5	
Zangemeister	1913	1614					2			
Sachs	1918	87			2					
Caldwell and Lyle	1921	22		2+	9					45
Harris	1924	27		1+	11					40
Hinselmann	1924	3988			2			2		
Kellogg	1924								15	
Döderlein	1925	26		1-15		4	40			
Corwin and Herrick	1926	44	20	15+		32	34	14	60	40
Nevermann	1927	60		1-26		13	10	2	10	
Donovan	1929	42	18							
Peckham	1929	74	6	3	38			13	56	44
Schmechel	1929	83			42			18	40	42
Breakey	1932	119		16	4	43	6			
Rucker	1932	113	7	3-28		13		8	27	
Young, Sym, Crowe	1932	67	19				20	10	36	
Kjelland-Mørdre	1935	48						13	44	43
Tillman	1936	47		2+			47	7	37	
Peters	1937	49	14	1-20	6	17		13	34	
Teel and Reid	1937	48		1-21		28	11	10	64	
Dieckmann and Brown		60	25	7+		37			60	40
Average			13		19	27	22	10	39	42

TABLE II. NONCONVULSIVE TOXEMIA

	YEAR	NUMBER CASES	HISTORY TOXEMIA %	YEARS FOLLOW-UP	CHRONIC NEPH. %	HYPER-TENSION %	HYPER. AND/OR ALBUM. %	RECURRENCE OF TOXEMIA %	NORMAL DELIVERY %
Baisch	1913	50					10		
Slemons	1913	18						17	
Harris	1924	85		1+	74				40
Hinselmann	1924							40	
Kellogg	1924	389			20	10		50	
Corwin and Herrick	1926	52	13	2-23		61		96	
Berman	1930	225			21		10	77	
Schultz	1932	124		1-28		8	3		
Young, Sym, Crowe	1932	239	32				20	43+	
Gibberd	1934	91		2-12	13			38	44
Peckham	1936	343		5+	40	23		56	
Tillman	1936	152				27	65	78	20
Peters	1937	144						41	46
Dieckmann and Brown		282	70	7+	0.5	40		70	30
Average			22		34	26	21	52	38

leave behind them marks, usually in the vascular system, that cannot be eradicated. Even if they do not manifest themselves immediately in progressive arterial or renal disease, they almost invariably flare up in subsequent pregnancies to cause further damage. There are no clinical distinctions between toxemias in this respect."

Corwin, Herrick and Peters are internists who have apparently forgotten that the incidence of vascular disease rises rapidly with increasing age. Furthermore, multiparity parallels increasing age. Our data, as well as those of Berman, indicate that with each succeeding pregnancy after one complicated by toxemia an increasing number of patients are left with a definite elevation of blood pressure and other vascular changes. Berman raises the query "does this perhaps point out that a great many cases of toxemia really react to a constitution which has a defective cardiovascular renal system, that with each pregnancy and the added wear and tear of life, definite inroads on the durability of this system have been made; rather than that the toxemia is the underlying cause of subsequent nephritis." We believe that this can be answered in the affirmative. Pregnancy in susceptible patients does cause a hypertension which may be present at first only during pregnancy, but after several pregnancies or a period of years, the blood pressure is constantly elevated. Pregnancy produces tremendous physical and chemical changes in the body, but these are usually transient, and only in the susceptible patient or in the normal patient under unusual circumstances does toxemia develop. However, in the majority of patients pregnancy is still a normal physiologic process, and it should not cause any permanent diseases. To illustrate this we have recently studied a small group of patients, all over 35, who have had 10 or more children. No evidence of anemia or of cardiovascular renal disease could be found.

The data in Table I show that from 1900 to 1927 the few studies of patients who had had eclampsia stated that chronic nephritis was found in 1.7 to 11 per cent of the cases afterwards. Two authors found no evidence of chronic nephritis but stated that a residuum of hypertension or albuminuria was present in 1.9 to 10 per cent of the patients after eclampsia. During this period only two authors stated that 5 to 15 per cent of the subsequent pregnancies would be toxemic, and a similar number stated that eclampsia would recur in about 2 per cent of the cases.

Corwin and Herrick, and Nevermann, in 1927, each emphasized the importance of a persistent hypertension and stated that 13 and 32 per cent of the patients, respectively, had an essential hypertension after eclampia. The former authors found that 61 per cent of the patients with nonconvulsive toxemia had a persistent hypertension.

During the past ten years many reports have been published and, while a number list hypertension as a sequel to eclampsia or preeclampsia, many still give chronic nephritis as the principal result. The most frequent findings at six months or longer post partum are hypertension and albuminuria which, we believe, are usually due to an essential hypertension. However, there is still much confusion about this matter. Thus, Stander continues to use the term "chronic nephritis" but now states that it may be the result of a previous acute glomerulo-

nephritis or of a nephrosclerosis. Bell attributes certain kidney lesions found at the autopsy of one patient to an eclampsia which had occurred seven years previously.

Meyer and Weiz in 1904 stated that in 35 autopsies of eclamptic patients chronic nephritis was found in 8 per cent. Acosta-Sison in 1931, in 38 autopsies of eclamptic patients, found chronic nephritis in 38 per cent. This report is the only one which is difficult to interpret, because it has been the experience of all that chronic nephritis is a very rare complication of eclampsia. Acosta-Sison does not list the criteria used for making a diagnosis of nephritis. It may be that he considered any lesion of the glomeruli, tubules, or renal arteries as evidence of chronic nephritis. It is worth noting that we have sections from the kidney of a 32-year-old patient who, in her fourth pregnancy, had albuminuria and a blood pressure which reached 180/110. The fifth pregnancy occurred the following year with the maximum blood pressure of 200/128. She died from a rupture of the uterus. The kidney sections have been examined by four pathologists, and, while all state that the kidney is not normal, none agree on the exact lesion which is present.

Teel and Reid examined 80 living patients who had had eclampsia from one to twenty-one years previously. Twenty-eight per cent had a blood pressure over 150, and 9 per cent had albuminuria. The urea clearance of only 1 out of 50 of these patients was less than 50 per cent of the normal. Ninety-four per cent of the clearances were more than 60 per cent. In no case was there definite evidence of renal impairment as a result of a chronic nephritis, and the authors conclude "if 'chronic nephritis' is a frequent sequel of eclampsia, it seldom progresses to the point of renal insufficiency."

McKelvey and MacMahon reported autopsy findings in 13 patients who died at varying periods after nonconvulsive toxemia. They emphasized the fact that, although their clinical diagnosis had been chronic nephritis in 10 of the patients, the autopsy findings revealed a nephrosclerosis and not the renal lesions of a chronic glomerulonephritis. Our clinical diagnosis would have been essential hypertension instead of chronic nephritis in 9 of the 10 patients.

Mengert reports that 45, or 0.9 per cent, of their obstetric patients had renal impairment. This was due to chronic glomerulonephritis in 15 and to essential hypertension in 30.

We have clinical records and autopsy sections from 21 eclamptic patients and 25 nonconvulsive patients. There was no evidence of chronic glomerulonephritis in any of these eclamptic patients, and only 5 of the nonconvulsive group had this disease. Another patient died of an acute nephritis. Those deaths not due to uterine hemorrhage or infection were due to cardiac failure, cerebral hemorrhage, or uremia. Thus, it is apparent from our work and the reports of Corwin and Herrick, McKelvey and MacMahon, Peters, and others that chronic glomerulonephritis during or after pregnancy is a rare complication.

Stander and Peckham made intensive studies of their toxemic patients one or more years after delivery and based their diagnoses on the findings at that time. They made no note in their early reports of how their findings checked with subsequent pregnancies. Peckham recently stated that 56 per cent of a group of patients who had had toxemia had a recurrence in a subsequent pregnancy. If the obvious pre-eclamptic patients were excluded, then 98 per cent had a recurrence. Tillman noted that 50 per cent of the patients with normal blood pressure and normal urine after a toxemia of pregnancy had a recurrence in the next pregnancy.

The data in the tables indicate that from 2 to 47 per cent of the patients who had eclampsia will have "chronic nephritis," essential hypertension, or a residual hypertension and/or albuminuria. The

latter group includes patients who have proteinuria, hypertension and proteinuria, or retinal pathology due to vascular disease. The averages for the groups named above are 19, 27, and 22 per cent, respectively. While there is no agreement as to the exact term for the lesion, published reports indicate that 50 per cent of the patients who have toxemia of pregnancy will subsequently have vascular renal disease.

The introduction by Stander and Peckham of the term low reserve kidney of pregnancy has been a real obstacle to progress in a study of the toxemias of pregnancy. It incorrectly emphasizes a nonexistent or, at the most, a minor renal sign (albuminuria). Thus much time and effort have been wasted with renal function tests. Furthermore, many patients with vascular renal disease were permitted to have repeated pregnancies because, according to the authors, no further damage to arteries or kidneys would result. The criteria for this condition, as originally described by the authors, were a maximum blood pressure of 160/90, a maximum albumin per day of 2 or 3 gm., and little or no edema. These signs were supposed to recur with each pregnancy but not to increase in severity. Then, each author, independently of the other, changed the criteria, so that now, according to them, the condition does not recur and usually develops late in pregnancy. Peckham limits low reserve kidney to primiparas and states that many of the patients who originally had this diagnosis now are grouped under vascular renal disease. The condition, as it is now described, is a mild pre-eclampsia. However, both authors conceive of pre-eclampsia as being a fulminating disease. They do not seem to believe, as we do, that there is a large group of pregnant patients with signs of mild toxemia who are all potential eclamptics.

Another approach to determine the seriousness of the toxemia of pregnancy has been to compare the subsequent mortality of patients who have had toxemia with that of patients who have had normal pregnancies. Stander and Peckham state that the mortality occurring within ten years of delivery in patients with "chronic nephritis" is 42.5 per cent. The average mortality for women between the ages of 30 and 40 years is 7.5 per cent. Mengert reports that the average yearly death rate for his group of patients with renal impairment was 7.1 per cent, which was two times that of women with chronic nephritis uncomplicated by pregnancy and nearly 18 times the death rate of the female population of childbearing age.

Gibberd states that 10 per cent of the patients with toxemia of pregnancy will develop chronic nephritis. Theobald has taken Gibberd's data and applied it to pertinent vital statistics for England and Wales. His study indicates that the incidence of Bright's disease is highest in the cities and by far the lowest in the rural districts, where the incidence of eclampsia and toxemia is highest. He also finds that the variation in mortality rates for Bright's disease between single and married women during the childbearing period and for fifteen years afterwards is so small as to be without marked statistical significance. Gibberd was discussing permanent vascular disease after toxemia of pregnancy, which he erroneously called "chronic nephritis." Theobald's data apply to acute and chronic glomerulonephritis or Bright's disease. He has also analyzed the mortality rates for deaths from vascular disease and, although he finds the death rates from cerebral hemorrhage higher in married than single, yet the rate is higher from all vascular disease in

single than in married women. He concludes that pregnancy and childbirth have but relatively little causal association with Bright's disease.

Osman has reported that of 24 patients between 25 and 45 years of age who had chronic nephritis 10 dated the onset to a pregnancy, and 7 of the 10 to a toxemia of pregnancy. Sixteen out of a similar age group of 18 dated their essential hypertension to pregnancy, and 11 had had a toxemia.

Breakey traced 119 patients who had had eclampsia and a similar group of patients after normal pregnancy. She noted that the rise of the blood pressure after eclampsia was more rapid and higher with increasing age than after normal pregnancy. There were 8 subsequent deaths. Five of these were due to nephritis, but the author does not distinguish between *nephrosclerosis* and *chronic glomerulonephritis*. She finds no decrease in fertility but does find an increase in the number of abortions. She also mentions the "toxemic sequence" of Young and states that eclampsia may begin or end it.

In addition to the recurrence of toxemia, Young recognized a "toxemic sequence." This has been described by other investigators but so far as we know, the term, which is an excellent one, is original with him. He finds that the incidence of abortion, premature labor, abruptio placentae and stillbirths is greater than normal in patients who have had a toxemia of pregnancy. Thus, the sum of these various conditions in normal patients is 10.2 per cent, and after a toxemia it is 23.2 per cent. The sequence after eclampsia is 44.7 per cent, pre-eclampsia 35.6, and abruptio placentae 32 per cent. Rucker also noted that the yield of live births after eclamptic pregnancies is less than after normal.

TABLE III. REPEAT PREGNANCIES AFTER TOXEMIA OF PREGNANCY

	NO. CASES	PRESENT PREGNANCY				
		NORMAL		TOXEMIA		TOTAL FETAL MORTALITY* %
		PATIENTS %	FETAL MORTALITY* %	PATIENTS %	FETAL MORTALITY* %	
Previous pregnancy, our hospital						
Eclampsia	8	63	0	37	67	25
Nonconvulsive toxemia	225	27	<2	73	20	15
Total	233	28	<2	72	21	15
Previous pregnancy, other hospitals						
Eclampsia	50	30	15	70	33	28
Nonconvulsive toxemia	57	11	0	89	15	15
Total	107	20	10	80	21	21
Grand Total	340	26	4	74	21	17

*Fetal mortality includes all fetal deaths from abortion, stillbirth, neonatal deaths, and therapeutic abortion.

Table III contains our data. We have had 56 eclamptic patients during the past seven years, but only 8 have had a subsequent pregnancy in our clinic. Two more are pregnant now. One has a hypertension and the other a normal blood pressure. The percentage of normal pregnancy is much higher than is usually encountered due to the few cases. Two hundred and twenty-five patients with nonconvulsive toxemia had two to four pregnancies in our clinic. Twenty-seven per cent of these patients had a normal subsequent pregnancy and 73 per cent had a repetition of the toxemia. According to our concept of pre-eclampsia, the condition can, and undoubtedly does, recur. However, if it did in any of our cases, it would, according to our classification, be diagnosed as vascular renal disease.

We have graded the severity of the toxemia according to the height of the blood pressure, amount of proteinuria, degree of edema and severity of the symptoms. As a rule, the blood pressure is higher with each pregnancy. The other symptoms and signs are usually less intense or, at the most, the same. Occasionally the toxemia may seem milder in a subsequent pregnancy. We have a few patients with unquestioned vascular renal disease who had toxemia in one or more pregnancies, then a pregnancy with little or no toxemia terminating in a live baby, and then severe toxemia with fetal death in subsequent pregnancies. This is a rare occurrence, and we have no explanation for it. We have 29 patients who have had toxemia with each pregnancy with fetal death each time due to marked placental infarction, retroplacental hematoma, or abruptio placentae. In a few instances a cesarean section at 32 to 36 weeks has given the patient her first live baby. Almost without exception these babies were below the average weight for the period of pregnancy, due to an abnormally small placenta or to infarction.

Convulsions are dramatic and if the patient states that she had them during pregnancy she probably had eclampsia. Seventy per cent of the patients who gave a history of a previous eclampsia had a recurrence of toxemia. Only two had convulsions twice, but the first attack in each case was in another hospital. The number of patients who gave a history of toxemia and had a normal pregnancy in our clinic is small because, despite their history, if the present pregnancy was normal, they were not referred to the toxemia clinic. Thus, we have no record of them. The percentage of recurrent toxemia is probably too high. If the figures for the eclampsia in our clinic are omitted, approximately 75 per cent of the patients who have had eclampsia or nonconvulsive toxemia of pregnancy will have a recurrence of nonconvulsive toxemia in a subsequent pregnancy. According to other clinics, the range is from 17 to 90 per cent recurrence with an average of 52 per cent.

An average of 13 per cent of the patients with eclampsia gave a history of a previous toxemia, and 10 per cent had a recurrence of the eclampsia. These figures are of special interest because it is in these patients that prenatal care should be intelligently administered and either a therapeutic abortion and sterilization performed or the eclampsia prevented by the usual methods. We have never seen a case of recurrent eclampsia, although two of our eclamptic patients stated that they had had eclampsia previously. Peters reports four patients with a recurrence of eclampsia and, in addition, one patient who had eclampsia seven times, another six times and a third three times. Teel reports 5 patients, each of whom had eclampsia twice. We have had one patient who had convulsions in a previous pregnancy with a repetition in another while under our care, but in the absence of hypertension, albumin and edema, and with a normal blood and urine chemistry, we made a diagnosis of epilepsy which was confirmed by the neurologic consultant. Another patient had a history of coma in her first pregnancy and with the second became quite drowsy just before labor due to a severe diabetes. In all probability, the previous coma had also been due to diabetes. Our concept of eclampsia is not incompatible with a recurrence, but if we saw

such a patient, we would first think of a hypertensive encephalopathy rather than eclampsia, then epilepsy, diabetes, and tetany from alkalosis.

The pre-eclamptic group comprised 75 per cent primiparas, 17 per cent secundiparas, and the remainder varied from the third to the thirteenth pregnancy. The recurrent toxemia group, composed of patients with essential hypertension, vascular renal disease, and chronic glomerulonephritis comprised 30 per cent primiparas for the first pregnancy in our clinic, and the remainder were multiparas most of whom had been pregnant three or more times. The parallelism between age, parity, and vascular renal disease has already been mentioned and is an important diagnostic point.

We have recently reviewed the histories of over 1,600 patients who had one or more toxemic pregnancies and found that 48.5 per cent have chronic disease of the vascular or renal systems. Over 40 per cent have a hypertension of 140 or more in the interval between pregnancies. The number of patients who have a hypertension or proteinuria in the interval between pregnancies is less than of those who have a recurrence of the toxemia. This is what one would expect. The blood pressure of patients who have a predisposition to vascular disease will, certainly while they are young, have a tendency to be within the normal range when the stimulus of pregnancy is absent. This is illustrated by the data given in Table IV. As the patients grow older, more and more will have a constant hypertension. Similarly, a higher percentage of the patients in the fourth decade, irrespective of parity, are going to have a hypertension during pregnancy than those in the second or third decades.

TABLE IV. CASE OF ESSENTIAL HYPERTENSION

DATE	WEIGHT KILO	BLOOD PRESSURE	ALBUMINURIA	
1923	49	130/70		
Jan., 1925	74	130/70	Negative	Pregnancy of 3 months' duration. Aged 25 years.
July, 1925	87	140/75		
July, 1925		170/100		3,280 gm. baby. 68 hour labor. Placenta contained hematoma and red infarcts.
Aug., 1925	73	130/75	Negative	
July, 1926	74	130/90	Negative	
Nov., 1928	73	160/100	Negative	Phenolsulphonephthalein 60 per cent in 2 hours.
Jan., 1930		208/120	Negative	Numbness of fingers and feet. Fainting spells. Dizziness. Phenolsulphonephthalein 65 per cent in 2 hours. Difficulty in talking. Various pains.
May, 1930	73	175/100		
June, 1930		160/100		
July, 1933	74	190/110	Negative	Urea clearance 105 per cent. U/B 16. Hemoglobin 14.1 gm. per cent. Serum protein 6.9 gm. per cent. Nonprotein nitrogen 33 mg. per cent.
Aug., 1938	74	234/134	Negative	Severe headaches. Urea clearance 86 per cent. U/B 22. Hemoglobin 15.3 gm. per cent. Serum protein 6.8 gm. per cent.

The "sequence" described by Young of abortion, stillbirth, and abruptio placentae is illustrated in Table III. We have added therapeutic abortion for toxemia and neonatal deaths, where there is no other cause than maternal toxemia. It is evident that over 25 per cent of the pregnancies after eclampsia and 15 per cent after nonconvulsive toxemia terminate without a living baby. If the patient has a recurrent toxemia, the fetal mortality is 21 per cent. If the pregnancy after a previous toxemia is normal, the fetal mortality is 4 per cent.

We have compared various data from the first pregnancy with those of the second and have listed the averages or means in Table V. Sixty-one patients had pre-eclampsia in their first pregnancy, but only 10 of these were graded as severe. Chemical analysis of the blood and urine after the second pregnancy was normal in all of the pre-eclamptic and 5 of the eclamptic patients. There is a greater decrease in hemo-

TABLE V. COMPARISON OF REPEAT PREGNANCIES AFTER TOXEMIA

	PRE-ECLAMPSIA PER CENT		VASCULAR RENAL PER CENT	
	TOXEMIC PREG.	NORMAL PREG.	1ST PREG.	2ND PREG.
Baby weight less than 2500 gm.	23	6	15	19
Hemoglobin less than 10 gm. per cent	20	2	11	6
Cell volume less than 30 per cent	15	2	8	1
Serum protein gm. per cent	5.8	6.3	6.7	6.4
Urea clearance less than 50 per cent	32	0	9	12
U/B ratio less than 20	5	0	10	11
Weight of baby—gm.	2770	3430	3146	2913

globin and serum protein concentration in pre-eclampsia than in normal pregnancy. Likewise, the urea clearance is decreased in the pre-eclamptic patient because of the oliguria and decreased concentration of urine urea nitrogen. The patients with severe essential hypertension or vascular renal disease were usually sterilized or given contraceptive instruction after their first pregnancy in our hospital. Thus, the comparison is chiefly between cases of mild and moderately severe vascular renal disease. However, although there are slight differences, they are too small to be of significance.

The statement has been made repeatedly that ophthalmoscopic examinations are of diagnostic value. All of our examinations of the retina have been made by experienced ophthalmologists, but the information has been of little value. Extensive pathology of the retina was found and yet the subsequent pregnancies were normal and vice versa.

We have been applying our theories to the clinic and hospital management of these toxic patients for over four years without any bad results. If the patient has an essential hypertension or vascular renal disease of mild degree, there is no interference. The patient is hospitalized if the blood pressure exceeds 200 mm., if the proteinuria exceeds 5.0 gm. per 24 hours, or if there is marked edema. The appearance of any of the above signs after thirty-two weeks indicates that the preg-

nancy should be terminated, primarily in the interest of the baby. The height of the blood pressure as a rule increases with each pregnancy, but our management has not caused any more renal damage, as measured by the urea clearance, than when we were more active in the use of therapeutic abortion.

Similarly, the pre-eclamptic patient is treated with a salt-poor or salt-free diet, bed rest, and sedation, unless there is an abrupt increase in blood pressure, edema or albumin, or cerebral, visual or gastro-intestinal symptoms appear. This means fewer cesarean sections and inductions of labor. The percentage of patients who recover completely is just the same as it was when we terminated the pregnancies in cases where the toxemia persisted for longer than a week.

The decrease in induction of labor, which was usually by mechanical means, and the decrease in cesarean section have resulted in a decided decrease in the morbidity and incidence of puerperal infection in these toxemic patients. The decrease in the use of a bag or pack for the induction of labor has also resulted in a decrease in the fetal mortality.

DISCUSSION

Normal pregnancy is characterized by an average gain in weight of 22 pounds, a slight rise in blood pressure not exceeding 130/80, and some pitting edema of the ankles. Some patients may have an excessive gain in weight, a hypertension or a proteinuria but no cerebral or visual symptoms. These patients have a mild pre-eclampsia because, as we have repeatedly observed, any one of them can within a period of twelve to twenty-four hours develop all the findings characteristic of severe pre-eclampsia or even eclampsia. Thus, we have a relatively large group of patients who are not normal. A small number of them develop severe pre-eclampsia and a still smaller number of the last named group develop eclampsia. We believe that pre-eclampsia and eclampsia are rarely fulminating. If the prenatal care has been intelligent, a severe toxemia may develop within twelve hours, but warning signs are almost invariably present for days or weeks. To date, no patient who has been followed in our toxemia clinic has developed convulsions or coma. We believe that the toxemia should be treated vigorously and, if necessary, the pregnancy interrupted *before symptoms appear.*

Pre-eclampsia and eclampsia may develop or recur if the proper conditions are present. Thus, we have had 424 patients who had one or more normal deliveries before they had a toxemic pregnancy. If we analyze these toxemic pregnancies to determine the cause, we may find, for example, that there were twins. Multiple pregnancy, probably because of the increased placental area and higher intraabdominal pressure, predisposes the patient to pre-eclampsia. Or there may have been a marked edema due to excessive ingestion or faulty excretion of water or salt. The patient may have had a marked anemia which predisposes to edema. Obesity may have been a factor. Hookworm disease, as reported by Wickramasuriya, increases the incidence of toxemia. Likewise, the impaired nutrition of our southern poor white and negro predisposes to toxemia.

A large number of patients first show an increased blood pressure during pregnancy which usually persists after the puerperium. Frequently these patients develop edema and proteinuria and occasionally cerebral and visual symptoms. If they happen to be young primiparas, they are usually said to have pre-eclampsia and, because the hypertension and occasionally the albuminuria persist after the puerperium, the signs are thought to be due to vascular renal pathology caused by the pre-eclampsia. We believe that these patients have a predisposition to hypertensive arterial disease by inheritance or by physical or mental instability (nervous and high strung). In such patients the normal physicochemical changes of pregnancy, together with the emotional stress and strain of pregnancy, result in the onset of hypertension which otherwise would not have appeared for years. This latter group of patients almost always give an abnormal response to the "cold test." The blood pressure is quite often not constantly elevated either during pregnancy or after the puerperium but may, during the course of the day, range from normal to hypertension levels, additional evidence of vasomotor instability. Ultimately it remains persistently elevated and the sequelae of hypertensive arterial disease develop in the kidney, heart, eyes, etc. The data listed in Table IV illustrate how pregnancy precipitated a hypertension in a susceptible individual and how within a few years the patient had a persistent essential hypertension. If this patient had had further pregnancies, the constantly rising blood pressure would have been attributed to the pregnancies. We have a number of similar cases.

For many years we accepted the belief that if "pre-eclampsia" lasted for a period of two or more weeks, permanent vascular renal damage would result in a high percentage of the cases. Since 1933, when we accepted the concept of hypertensive arterial disease as a complication of pregnancy, we have come to believe that if a marked hypertension, albuminuria, and edema persist for two weeks, despite adequate treatment, the primary disease is not pre-eclampsia but an essential hypertension or glomerulonephritis with perhaps a superimposed symptom complex of pre-eclampsia. Certainly, patients with severe pre-eclampsia extending over a period of weeks can have a normal subsequent pregnancy.

The incidence of abruptio placentae in our clinic is 0.6 per cent. It is 3.5 per cent in a toxemic pregnancy, where the preceding one was normal, and 5.5 per cent in the vascular renal or recurrent toxemia group, where the disease was mild enough to permit a second pregnancy. We believe that the incidence is much higher in the severe vascular renal patient and that placental infarction, retroplacental hematoma or abruptio placentae account for the major portion of fetal deaths in these patients.

The eclamptic patient, who has a recurrence of toxemia or has permanent damage of the arteries and kidneys, according to our concept, either had the eclampsia syndrome superimposed on a susceptible vascular system or, what is more probable, the convulsions were those of a hypertensive encephalopathy. During the eclamptic attack it would be,

as a rule, impossible to distinguish which type was present. If we grant that there are two types of eclampsia, many of the conflicting results, especially as to treatment, can be satisfactorily explained. Thus, one would expect that heavy sedation would stop the convulsion of the hypertensive type and that delivery would not be urgent. The true gestational type of eclampsia would not respond so readily to sedation and would require early termination of the pregnancy. A similar explanation is tenable for pre-eclampsia. The fact that a certain percentage of patients who have had severe eclampsia or pre-eclampsia have no permanent vascular or renal damage offers excellent support to our theory.

CONCLUSIONS

Eclampsia.—Subsequent pregnancies will be normal in 40 per cent of the cases and complicated by a recurrence or exacerbation of the hypertension, edema, or albuminuria in 40 per cent.

Less than 10 per cent will have a recurrence of the eclampsia.

Over 37 per cent of the patients had vascular renal disease, indicated usually by a hypertension. No evidence of chronic glomerulonephritis was found in any of our eclamptic patients.

Nonconvulsive Toxemia of Pregnancy.—Subsequent pregnancies will be normal in at least 30 per cent and probably 40 per cent of the cases, and complicated by a recurrence or exacerbation of the hypertension, edema or albuminuria in 50 to 70 per cent.

Over 40 per cent of the patients had vascular renal disease, evidenced usually by a hypertension. Renal impairment, as indicated by a urea clearance of less than 50 per cent and due to nephrosclerosis, occurred in 2 per cent. Chronic glomerulonephritis was present in 0.5 per cent.

We believe that true eclampsia and pre-eclampsia do not cause permanent vascular or renal damage and that where such damage occurs, either the condition was not eclampsia or pre-eclampsia or these diseases were superimposed on a patient with a predisposition to hypertensive arterial disease.

The fetal mortality, including all fetal deaths from abortion, stillbirth and neonatal deaths is over 25 per cent in all pregnancies after eclampsia and 15 per cent after nonconvulsive toxemia. In toxemic pregnancy after eclampsia it is over 40 per cent and in recurrent toxemia it is over 20 per cent. Normal pregnancies after eclampsia or pre-eclampsia have a 5 per cent fetal mortality.

Eclampsia and pre-eclampsia are diseases peculiar to pregnancy. They rarely occur without premonitory signs of excessive or too rapid gain in weight, edema, abnormal increase in blood pressure, hypertension, or proteinuria. Either disease may recur, but such a repetition should always suggest vascular renal disease.

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DISCUSSION

DR. R. D. MUSSEY, ROCHESTER, MINN.—I quite agree with Dr. Dieckmann's classification of the toxemias. In the first place there is the acute group, and in the second, the chronic group. In the acute group we have the pre-eclampsia which can proceed from mild to severe stages and may culminate in eclampsia. I believe the low reserve kidney should be classified as a mild toxemia. I believe the classification of the chronic cases which Dr. Dieckmann has outlined, and which takes into consideration a pre-existing vascular or vasculorenal damage, is correct, and that on top of the previous vascular damage we may or may not have a superimposed toxemia during pregnancy. This explains the lack of acute toxic symptoms in some of these patients who have hypertension. However, in this group of patients who enter pregnancy with hypertension and in whom no vascular or renal damage can be found by examination, toxemia is more likely to develop.

The toxemias of pregnancy, at least a great many of them, depend on a preexisting tendency in the individual to develop vascular diseases. To show this the so-called ice water test is of some value. In employing it in our group of apparently normal pregnant women in the first trimester, it was found that of the patients not reacting to the test very few developed toxemias later. About 30 per cent of the patients who showed an undue response to this test developed signs of preeclamptic toxemia.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I am still not satisfied with the current classification of the so-called toxemias of pregnancy. We have the terms pre-eclamptic and eclamptic toxemia. They are clinical terms. Then we have the classification of acute glomerular nephritis and chronic nephritis, which are pathologic terms. Now we have another way of describing these conditions by a man's name. Some sort of classification ought to be invented whereby we throw out all the clinical classifications and use only a pathologic classification, but at present I cannot see how we can do this.

DR. DIECKMANN (closing).—Dr. Pendleton states that he does not approve of our classification because it is a mixture of clinical and pathologic terms. This classification is not original with us, but has been used by Herrick and co-workers, Stieglitz, Kellog and co-workers, and others. It is of value in that at least one-half of all patients with so-called "toxemia of pregnancy" can be removed from this unknown group. The probable fetal and maternal mortality are also known for patients with hypertensive arterial disease. Progress will be made at a faster rate if we accept knowledge already at hand instead of waiting for a complete explanation of toxemia of pregnancy.

CYSTOGRAPHY IN THE DIAGNOSIS OF PLACENTA PREVIA*

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THE possibility of developing a method of precision for the roentgenologic diagnosis of placenta previa has been explored from several angles, but thus far no completely satisfactory procedure has been devised. This study was planned to present a contribution to the elucidation of this problem.

Menees, Miller, and Holly[1] published their preliminary article on amniography in 1930. The method advocated roentgenography after the transperitoneal injection of strontium iodide into the amniotic cavity. Viewed in profile, the placenta presented a crescentic filling defect in the amniotic cavity. Further contributions to this method were made by Kerr and MacKay[4] and Burke.[10] However, the method has been virtually abandoned because of its potential danger, and because it was occasionally unsuccessful.

Ehrhardt[2] in 1932 suggested the intravenous injection of thorotrast, a radiopaque medium useful because it was absorbed by the reticulo-endothelial elements in the placenta. Although this method gave satisfactory visualization in the rat, it failed to do so in the human being. A further disadvantage is the relatively high toxicity of thorotrast.

Direct visualization of the placenta in an ordinary anteroposterior radiograph was advocated by Powell and Snow,[5] in 1934. They believed they were able to detect the shadow of the placenta when the uterus was radiographed from the correct angle. Their report included no case of placenta previa, but was based on the visualization of the placenta implanted in the fundus. As Ude and Urner[8] pointed out, detection of the placenta in the usual fundal position eliminates placenta previa.

In many radiologic laboratories it has proved difficult to detect the placenta on a flat film without the use of some contrast medium. Such an aid was offered by Ude, Weum and Urner,[6] in 1934, who outlined the soft tissue space between the fetal skull and the bladder by instilling sodium iodide solution into the viscus. Their criterion for diagnosis of central placenta previa was symmetrical increase of the distance between skull and bladder, or, for marginal placenta previa, the unilateral widening of this space. The following year, Ude and Urner[18] reported fourteen accurately diagnosed cases of placenta previa. The difficulties of the cystogram method in other than vertex presentations was demonstrated and the differential diagnosis of other potential causes of variation of the soft tissue space between skull and bladder was outlined. Later, these authors[18] presented four additional cases and noted the possibility of diagnosis in breech and transverse presentations. The recommended technique consisted of introducing 40 c.c. of 12.5 per cent aqueous sodium iodide solution into the empty bladder and taking an anteroposterior film centered on the mid- or lower abdomen.

Numerous investigators[7, 11-17, 19] have reported encouraging results with the original method and technique. Several minor changes have been recommended, e.g., McDowell[12] suggested a second plate after withdrawal of 10 to 15 c.c. of the opaque

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

solution should the first film reveal overlapping of the fetal head by the bladder; and Wells[16] favored a weaker solution (5 per cent) of sodium iodide. Several observers have stressed the importance of cleansing the lower bowel prior to taking the cystogram.

Despite the advance in the diagnosis of placenta previa offered by roentgenography, many difficulties remain, including interpretation of the cystograms and the lack of adequate definition of the boundary between normal and abnormal. In fact, certain of the published cystograms appear to give little evidence of the presence of placenta previa, although presented as clinically proved cases.

It is not surprising, in view of these difficulties, that Hundley and co-workers[9] in 10 patients wrongly interpreted the criteria for diagnosis and were inclined to discredit the method. Beck and Light[17] in a series of 71 patients with last trimester bleeding and with vertex presentations, report that the method was accurate in 63 patients (88.7 per cent) and noted that the accuracy was greater in excluding placenta previa (92.6 per cent) than in diagnosing (76.5 per cent) this condition.

In order to overcome, if possible, some or all of these difficulties the present study was undertaken and developed to determine the best type of contrast medium and the most suitable positions of the patient during roentgenography. A simple scheme of comparative measurements is also proposed.

SUBJECTS

One hundred and twenty patients, each in the last trimester of pregnancy and selected at random or because of clinical indications, were studied. The diagnosis of placenta previa in the patients with antepartum bleeding was confirmed by vaginal examination during labor, or in one patient, by inspection during cesarean section. In the entire series, 23 patients had some vaginal bleeding in late pregnancy; 5 had placenta previa and 1 had low implantation of the placenta.

TECHNIQUE

In general, no special preparation for cystography was necessary but an occasional patient needed an enema. Invariably the medium was instilled into the empty bladder and the catheter removed before exposure. The roentgenograms were taken on Dupont film, using a Snook machine fitted with a Potter-Bucky diaphragm with intensifying screens and operating at 50 milliamperes and 74 to 78 kilovolts. The distance from film to tube was 33 inches, and the time of exposure was three seconds.

Media.—Three contrast media were used: sodium iodide in 2.5, 12.5, and 25.0 per cent aqueous solutions, skiodan in 10.0 and 40.0 per cent aqueous solutions, and air. The weak solutions of sodium iodide gave poor delineation while the higher concentrations, although giving excellent visualization, irritated the bladder. The 12.5 per cent solution, recommended by Ude and Urner, proved to be the most satisfactory.

Skiodan in 10.0 and 40.0 per cent solution outlined the bladder clearly but was costly. The liquid media in optimum quantities gave the relation of the bladder to the fetal skull, but failed to delineate clearly the space between these structures. More than 80 c.c. obscured the relations by causing the bladder and fetal skull shadows to overlap, thus entirely obscuring the space.

On the other hand, air, as the contrast medium, not only outlined the bladder smoothly, but also pictured in sharp relief the soft tissues intervening between

the white shadow of the fetal skull and the black of the bladder (Fig. 1, *A*). Forty to 250 c.c. of air were tried but 100 c.c. gave optimum results. With less than this amount, the air tends to collect on one side of the bladder. Larger quantities, however, did not obscure the space between the bladder and the fetal skull. The air cystograms likewise permitted measurements of the vesicocranial space.

Position.—The majority of previous workers took only an anteroposterior film with the patient in the supine position.* One investigator[8] tried but discarded the direct lateral exposure. In an attempt to obtain the theoretical advantage of

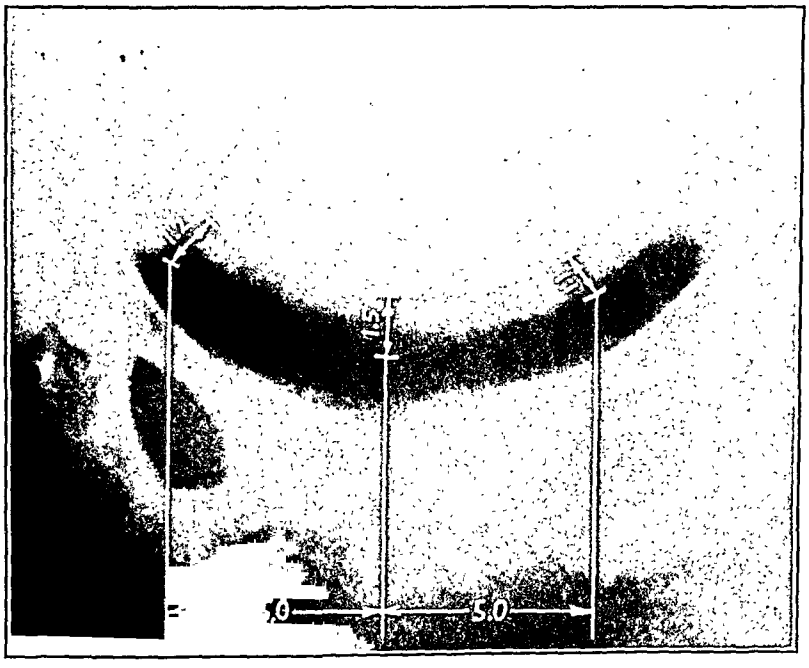


Fig. 1, *A*.—A normal anteroposterior air cystogram illustrating the method of obtaining measurements of the vesicocranial space.

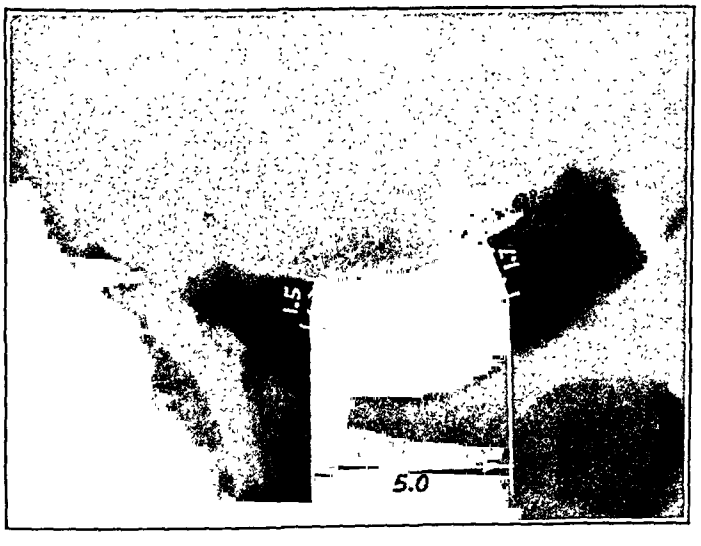


Fig. 1, *B*.—A normal semilateral air cystogram to illustrate the method of obtaining measurements of the vesicocranial space.

*Following the completion of the present experimental study, the authors noted in a recently published article by Ude, Urner and Robbins a reference to the employment of the oblique film. In a personal communication from Aurelius and Schulze, it was stated that the oblique film was of assistance in arriving at a correct diagnosis.

viewing the soft tissue space through another plane and to obviate the disadvantages of direct lateral exposure, films were taken with the patient in the semilateral position. This was accomplished by tilting the pelvis thirty-five degrees to either side and centering on the bladder (Fig. 2). By these means an excellent silhouette of the vesicocranial space is obtained without interference by bone, inasmuch as the rays pass through the greater sciatic notch. However, it must be emphasized that exposures in *both* semilateral positions should be used, since only a single side of the space is demonstrated in each. This position proved especially valuable in two patients with placenta previa, since the anteroposterior films showed no positive evidence of this condition (Fig. 3, *A*), and the diagnosis was made entirely from interpretation of the semilateral films (Fig. 3, *B*). It appears from writ-

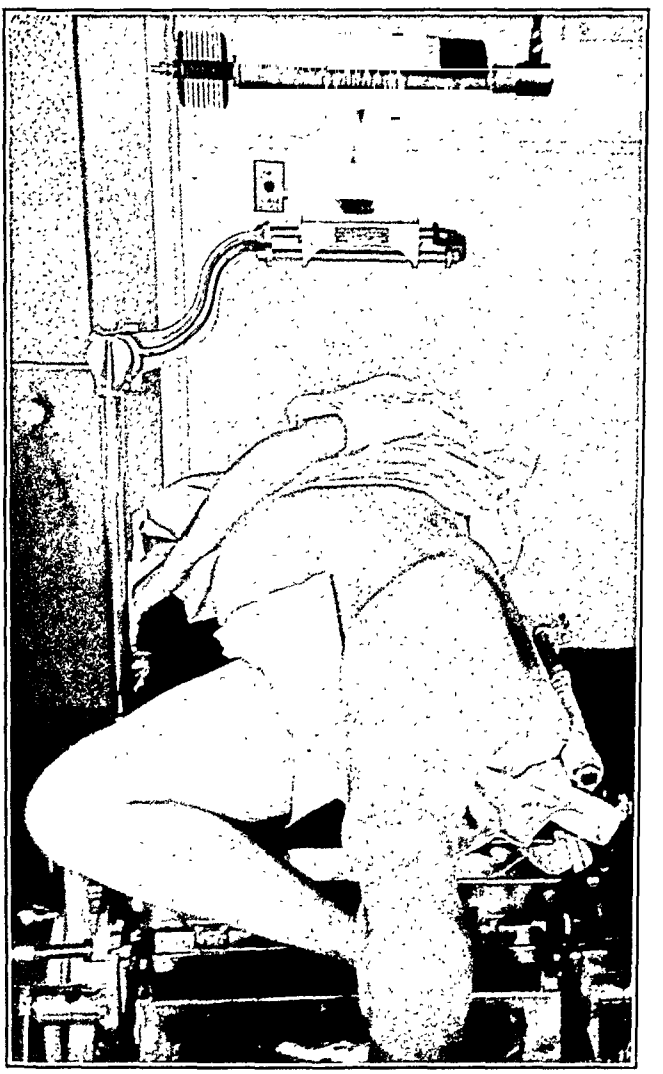


Fig. 2.—Patient in right semilateral position.

ten reports that failures to diagnose placenta previa when the placenta was implanted posteriorly may have been due to the use of the anteroposterior film alone. In addition to increasing the percentage of accurate diagnoses, the semilateral view should aid in better localization of the placenta.

Inasmuch as a floating head might easily lead to a false interpretation, fundal pressure was used to force the head toward or into the pelvis. However, this force was inevitably variable and destroyed normal relationships if the shadow of the head tended to overlap the symphysis. This potential error was exemplified in one

patient on whom the anteroposterior cystogram revealed a central placenta previa (Fig. 4, *A*), whereas in a second film (Fig. 4, *B*) taken during application of manual pressure, the relationships appeared normal. The erect position, utilizing the force of gravity on the fetus, was discarded because of overlapping and of roentgenologic difficulties. The use of the semi-erect position (feet down at an angle of forty degrees) solved the problem by providing optimum gravitational force.

Adopted Method.—The adopted technique included injection of 100 c.c. of air into the emptied bladder and taking three films, one in the anteroposterior semi-erect (forty degrees) position and one in each semilateral position with the feet down at an angle of five or ten degrees.



Fig. 3, *A*.—Patient I. K. Anteroposterior film shows no evidence of placenta previa, although patient had a marginal type.



Fig. 3, *B*.—Right semilateral view of vesicocranial space in Patient I. K., showing sharp deflection of posterior horn of bladder indicative of a posterior marginal implantation of the placenta.

Measurements.—On the roentgenograms, the space between fetal skull and bladder was measured in order to establish standards of normality. The perpendicular distances between the two arcs were measured; on the anteroposterior cystogram in the midline and bilaterally at 5 cm. distance (Fig. 1, *A*), and on the semilaterals at the symphyseal joint and 5 cm. posterior to this point (Fig. 1, *B*). It was realized, of course, that the measurements obtained were not absolute but were subject to distortion according to the size of the patient. Normal patients (Table I) generally presented measurements which closely approximated the average for the group, but occasional marked variations from the average considerably extended the range. On the other hand, in 4 patients with placenta previa (Table II) one or two measurements greatly exceeded the upper limits of normal, although the other values were well within the established range. The cystograms of the fifth patient (A.H.) were diagnosed as being suspicious for placenta previa because of variations in the width of the shadow rather than because the various measurements exceeded the upper limits of normal.

TABLE I. MEASUREMENTS IN CENTIMETERS OF THE SPACE BETWEEN BLADDER AND FETAL SKULL IN PATIENTS WITHOUT PLACENTA PREVIA

	POSITION	MEDIUM	NUMBER OF PATIENTS	RIGHT		MID		LEFT	
				AVER.	RANGE	AVER.	RANGE	AVER.	RANGE
Antero-posterior	Supine	Air	61	1.3	0.7-2.2	1.3	0.8-2.1	1.4	0.7-2.3
	Semi-erect	Air	32	1.0	0.7-2.1	1.1	0.7-1.8	1.1	0.7-1.9
				ANTERIOR		POSTERIOR			
				AVER.	RANGE	AVER.	RANGE		
Semilateral	Right	Air	74	1.2	0.7-2.2	1.7	0.8-2.8		
	Left	Air	16	1.1	0.8-1.7	1.4	0.7-2.3		

INTERPRETATION

This form of roentgen diagnosis of placenta previa depends upon visualization of the space between the fetal skull and the bladder. Normally this vesicocranial space is occupied by the bladder wall, peritoneal fold, uterine wall, membranes, and fetal scalp; in placenta previa it is widened by the interposition of some portion of the placenta. Normally in all views of this space, the arc of the bladder shadow follows closely the arc of the fetal head. Measuring the width of this space in a series of patients without placenta previa has established certain adequate standards of normality, the upper limits of which are considerably above the 1.0 cm. limit imposed by some observers. It has, however, been impossible to establish standards for the diagnosis of placenta previa, because of the scarcity of patients with this abnormality. While diagnosis by this plan of film mensuration awaits further confirmation, it is clear that in the anteroposterior film sudden or gradual widening of the soft tissue space, unilaterally or symmetrically, strongly suggests an abnormal position of the placenta. In the semilateral view similar criteria obtain for positive diagnosis, i.e., sharp deflection of the anterior or posterior horn of the visualized bladder, and consequent widening of the soft tissue shadow (Fig. 3, *B*). In both views, with depression of the bladder arc, there is symmetrical or unilateral displacement upward of the presenting part. Naturally these gross variations in the relations of the fetal head to the bladder can be expressed numerically (Table II).

With experience, the interpretation of individual films becomes increasingly clear. Ninety-five per cent of this series were readily interpreted, while with vertex presentations only 3 per cent presented any difficulty. Abnormal presentation, fetal anomalies, physical defects in the mother, and technical errors in exposing the films accounted for those cystograms which were not amenable to interpretation. Abnormal presentations do not invariably preclude interpretation; this is true particularly in breech presentation. However, accuracy is greater in excluding placenta previa than in its diagnosis (Fig. 5).

TABLE II. MEASUREMENTS IN CENTIMETERS OF PATIENTS WITH PLACENTA PREVIA COMPARED WITH MEASUREMENTS OF PATIENTS WITHOUT PLACENTA PREVIA

PATIENTS WITH PLACENTA PREVIA	MEDIUM	SUPINE			SEMI-ERECT			RIGHT SEMILATERAL		LEFT SEMILATERAL	
		RIGHT	MID	LEFT	RIGHT	MID	LEFT	ANTERIOR	POSTERIOR	ANTERIOR	POSTERIOR
G. W.	Sodium iodide	1.0	3.1	5.2	-	-	-	-	-	-	-
I. K.	Sodium iodide	0.0*	0.0	1.4	-	-	-	0.0	3.8	-	-
C. S.	Sodium iodide	1.9	2.4	1.6	0.9	2.4	2.2	0.0	3.4	-	-
H. S.†	Air	1.9	1.8	2.1	-	-	-	2.0	4.5	-	-
A. H.	Air	-	-	-	1.2	1.6	2.0	1.4	2.6	2.0	1.8
Upper limits of normal	Air	2.2	2.1	2.3	2.1	1.8	1.9	2.2	2.8	1.7	2.3

*Measurement 0.0 means contiguous.
†Patient had low implantation of placenta.

In this series 5 out of the 23 patients with antepartum bleeding had placenta previa. Four were accurately diagnosed from cystograms, one (A. H.) being classified as only suspicious. In one patient with ante-partum bleeding and breech presentation, the cystogram was not conclusive, but at delivery the patient had placenta previa. In the remaining 18 patients with bleeding, placenta previa was accurately eliminated.

Among the 97 patients without clinical suspicion of placenta previa, 3 presented radiographic data which were diagnosed as positive. One of these left the hospital prior to delivery. Another began to bleed during the first stage of labor and ex-



Fig. 4, *A*.—Patient G. W. Anteroposterior cystogram diagnosed as indicative of placenta previa. Central placenta previa found at time of cesarean section.



Fig. 4, *B*.—Anteroposterior cystogram taken on G. W. with manual pressure applied to fundus. This pressure obliterates all criteria diagnostic of placenta previa.

amination revealed a low placental implantation. The third patient had no bleeding, and examination of the membranes indicated a normal implantation. The interpretation of this film was obviously erroneous.

Compound presentation, pelvic tumor, intrauterine blood clots, distended bowel, and contracted pelvis are conditions which should be ruled out before arriving at a positive roentgenologic diagnosis of placenta previa. Occasionally a film is encountered in which the bladder and head are displaced to opposite sides of the bony pelvis (Fig. 6). This occurs especially in patients with roomy pelves, or with partial or complete engagement of the fetal head, and may lead to error. Recalling that a mass on one side of the pelvis will displace both head and bladder to the opposite side will ordinarily permit an accurate interpretation.

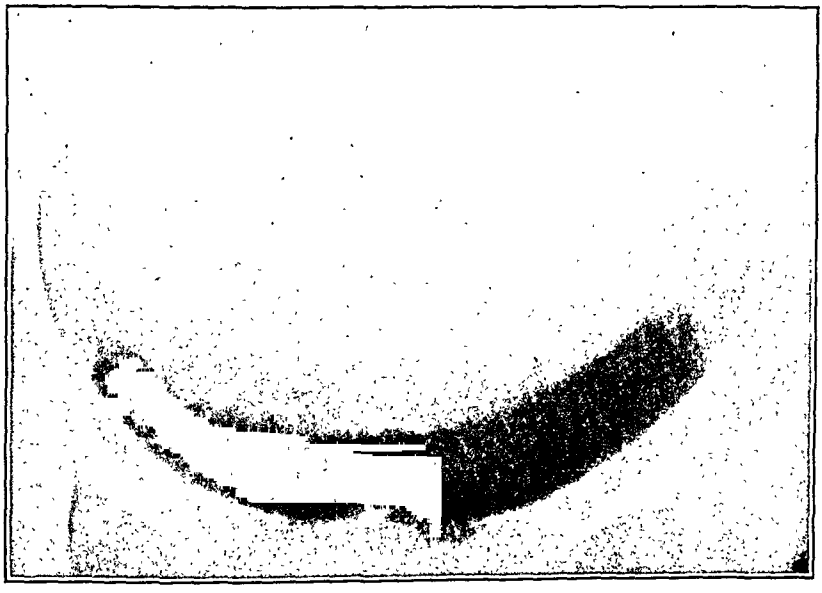


Fig. 5.—Air cystogram of patient with breech presentation illustrating how this presentation does not necessarily rule out accurate interpretation. This film shows no evidence of placenta previa.

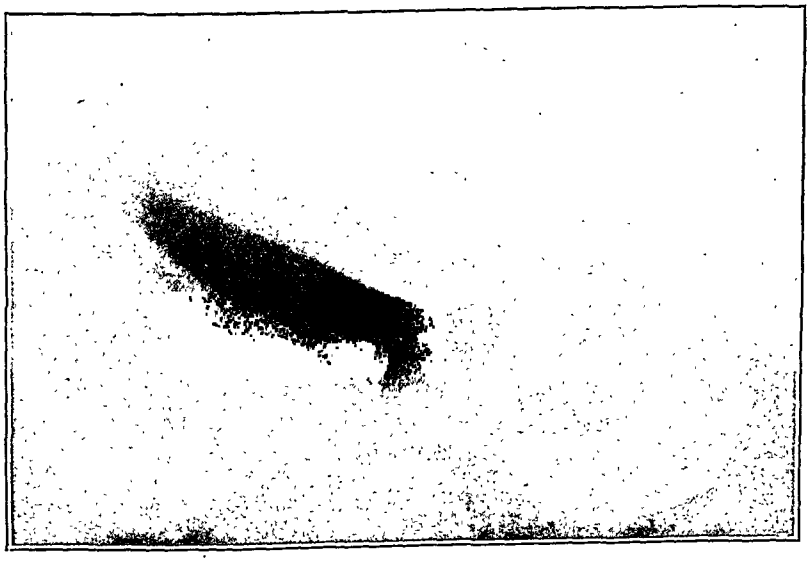


Fig. 6.—Normal anteroposterior cystogram illustrating possible danger of false interpretation because of assymetry due to head displacing bladder laterally.

CONCLUSIONS

1. Air cystograms provide a clearer, simpler, and more accurate method of delineating the bladder than do cystograms made with liquid media because the space between the bladder and fetal skull is not obscured.

2. The combination of semilateral and semi-erect anteroposterior positions offers greater accuracy in the diagnosis and localization of placenta previa than does the use of the anteroposterior position alone.

3. Measurements of the vesicocranial space in 5 patients with placenta previa, as well as standards established from measurements of patients without placenta previa, are presented.

4. The high degree of accuracy of the cystographic method for diagnosing placenta previa is confirmed.

The authors wish to thank the members of the Department of Radiology for valuable suggestions.

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DISCUSSION

DR. HARLEY E. ANDERSON, OMAHA, NEB.—This procedure is extremely valuable in ruling out placenta previa. In vertex presentation with no space intervening between the fetal skull and bladder, it can be accepted that the placenta is normally implanted.

It has been hoped also that this procedure might differentiate the types of placenta previa and in our experience this has been possible. In the marginal and lateral implantation there is but a slight space intervening between the fetal skull and the bladder on the side where the placenta is found and the bladder does not show the usual flattening that is found in the central implantation. In the centrally implanted placenta on the other hand, the head is usually separated from the superior surface of the bladder by some 2 to 4 cm. In addition, the bladder has a characteristic contour, consisting in an increased concavity of its superior margin which is very likely produced by the pressure of the placenta against the bladder.

We do not believe that it is the presenting part which produces pressure against the bladder but rather that the pressure is produced by the placenta itself against the bladder. In substantiation of this statement, we have had one case of transverse presentation complicated by a centrally implanted placenta previa. The

diagnosis was made on the characteristic flattening of the bladder which was undoubtedly produced by the pressure of the placenta upon the superior surface of the bladder and not by the presenting part inasmuch as there was none in the pelvis.

It has been rather conclusively demonstrated that cystography is of no value in a differential diagnosis between ablatio placentae and placenta previa for the reason that there is an appreciable space between the fetal head and the maternal bladder in both instances. The cause of this space in ablatio placentae is very likely the blood which has gravitated to the lower uterine segment. However, the bladder shadow is thicker and does not give the usual flattening that is so characteristic in placenta previa. This should be of help, but clinical judgment in premature separation of the placenta should still play the major role.

DR. OWEN F. ROBBINS, MINNEAPOLIS, MINN.—With regard to measurements, I have had occasion to measure the craniovesical space in a number of instances, although I recognize that the measurements presented by Drs. Prentiss and Tucker may be more accurate. Abnormal presentations were not considered in my group, so there were 175 cases studied and corrected for disproportion by the Thoms' grid. I centered the tube over the symphysis, the patient was prepared and the plate and tube left in situ, then the Thoms' grid was placed 2 cm. below the symphysis. After the grid has been placed, a flash exposure was taken. This picture I am showing was taken by means of that technique. In this next slide, you see the craniovesical space is between 0.2 and 1.8 cm. with a few beyond 2 cm. These were taken at seven months. The next slide shows the patients at eight months and at term. My figures are close to those of Drs. Prentiss and Tucker. The space is normally greater than 1 cm., especially in the seventh month of pregnancy. In my series I incidentally encountered a patient with a central placenta previa, later proved by cesarean section. The measurements were 6.3 and 2.6 cm.

I might mention the negative value of x-rays in breech presentation. In my series there were 19, ten of which could be read as negative and placenta previa ruled out.

DR. T. W. WEUM, MINNEAPOLIS, MINN.—In the series of cases reported by Ude, Urner, and myself I was fortunate to have a case referred to me in which clinically we made a diagnosis of placenta previa at about seven months. Roentgenologic examination was made principally to determine the maturity of the baby, so that a section could be performed at that time and have a viable baby. We were pleased to find the roentgenogram showing a distinct mass lying between the partially filled urinary bladder and the head of the fetus. Four days later I was able to verify the roentgenogram by the operative findings. This led us on to further study by using a contrast medium in the urinary bladder.

DR. PRENTISS (closing).—There are three points which I wish to emphasize in our study. First, air makes an excellent contrast medium without obscuring any more dense shadows on the x-ray film as is illustrated by this first film. The bladder is saucered when depressed by the oncoming head, and therefore the edges of the saucer would obscure the craniovesical space if an opaque medium were used to outline the bladder. However, air, being less opaque than the tissues in question, does not obscure them, and therefore the craniovesical space is outlined in sharp relief.

Second, the clarity of the outline and contrast obtained by air makes it the more desirable medium to use in obtaining accurate measurements of the craniovesical space.

Third, failure to diagnose the presence of a marginal placenta will occur repeatedly unless views of the posterior part of the craniovesical space are obtained, as was illustrated by the films of two of the patients presented. Films obtained in the right semilateral position silhouette the left posterior portion of the craniovesical space. The opposite is true of the left semilateral position. Both must be obtained before marginal implantation of the placenta may be excluded by means of cystograms.

THE CLINICAL SIGNIFICANCE OF ENDOMETRIOSIS*

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THE term "endometriosis," familiar to surgeons and gynecologists, was introduced by Sampson[18-20] to describe peculiar lesions which occur in adult women and which are found almost exclusively in the pelvis or lower abdomen. Regardless of their particular location, these lesions have as their common denominator the presence of endometrial tissue which is indistinguishable pathologically and physiologically from that found within the uterine cavity. They are neither tumors in the ordinary sense of the word nor products of inflammation, although they have some of the characteristics of both orders of pathologic phenomena.

Endometriosis appears to be associated frequently with primary or secondary sterility and in a large proportion of cases there is associated disease of the uterus or adnexa; it is also interesting to note that in many patients in whom this condition is found, an abdominal or a pelvic operation has previously been performed. Thus, in a recent study at the Mayo Clinic, an incidence of pregnancy of only 56.5 per cent was found; previous surgical procedures had been carried out in 54.2 per cent of patients and associated disease of the uterus or ovaries or both was found in over 50 per cent.

Aberrant endometrium may appear within the uterus, in the pelvic tissues or organs and finally in locations which are distant from the uterus. In the uterus, the endometrial productions may be within the muscle, under the peritoneum or in the region of the cervix. External locations may be the tube, ovary, the rectovaginal septum, the cul-de-sac, the bladder, rectum, the uterine and ovarian ligaments, the pelvic lymph glands; more rarely the large or small intestine, the appendix, the inguinal region, the labia, the umbilicus, laparotomy scars or the lungs may be involved. In all of these various locations, the pathologic findings are identical; there are glandular tubules identical with the epithelial diverticula of the uterine mucosa, formed of simple columnar epithelium, which is often ciliated. Around these epithelial formations one finds a connective tissue containing nuclei which resemble those in the subendometrial tissue of the uterus; there may also be smooth muscle fibers between the epithelial islands, the whole recalling a miniature uterus. In addition to this morphologic resemblance, the endometrial formation, under the influence of the ovarian hormones, follows the menstrual cycle of the uterus; hemorrhage occurs, cysts form and rupture may ensue. Moreover, during pregnancy, the ectopic tissue undergoes formation of decidua, involution occurring subsequently.

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minnesota, October 6 to 8, 1938.

The number and the diversity of the hypotheses which purport to explain the pathogenesis of the mentioned phenomena are ample evidence of the uncertainty which still enshrouds the origin of endometriosis. It must, however, be borne in mind that in this condition several distinct pathogenic factors may operate, just as in carcinoma generalization may occur by virtue of lymphatic, vascular, and contiguous dissemination. In a general way these various hypotheses have been grouped into the three following classes: (1) embryonic, (2) metaplastic, and (3) migratory.

HYPOTHESES OF EMBRYONIC PATHOGENESIS

The Wolffian hypothesis of von Recklinghausen and the Müllerian hypothesis, which was championed especially by Cullen, could at best explain only the endometriomas in the immediate vicinity of the uterus, where these embryonic residues could conceivably exist. These hypotheses are chiefly of historical interest today.

HYPOTHESES OF METAPLASTIC PATHOGENESIS

Iwanoff first suggested a serosa-epithelial metaplasia of the peritoneum; Meyer, Lauche and others have developed this hypothesis. Supposedly, under the influence of an inflammation or of an ovarian hormonal action, the pelvic peritoneum might form tubular invaginations which would sink more or less deeply into the tissues of subjacent organs. Simultaneously, the flat endothelium of the involved peritoneum might become transformed into columnar epithelium, thus producing an adenomatous appearance. In addition, around these glandlike cavities, the connective tissue might take on the characteristics of the subendometrial tissue and muscle fibers might appear. Pick conceived a like process involving the germinal epithelium of the ovary. Others have suggested a metaplasia of lymphatic endothelial tissue.

Although the common celomic origin of the peritoneum, the ovary, and the Müllerian ducts might be consistent with these hypotheses, it seems that they assume profound histologic and physiologic changes for adult peritoneum; it is clearly established that the ovarian hormones have an important effect on fully developed endometriomas, but it is certainly not established that they might initiate the development of these lesions. It must be stated, however, that some writers have assumed embryonic rests underlying the mesothelial change into adult endometrial tissue.

HYPOTHESES OF MIGRATORY PATHOGENESIS

These hypotheses assume that the endometrial tissue in endometriosis has its origin in the uterine mucosa.

Contiguity.—It is generally accepted, as originally suggested by Cullen, that adenomyomas of the uterus illustrate an invasion of the uterine musculature by its endometrial lining. It is also recognized

that such adenomyomas may be directly traced to the subserosal tissue or to the cul-de-sac, bowel or abdominal wall, as emphasized by Haselhorst. This, however, does not obtain in most cases of endometriosis.

Implantation.—Sampson's hypothesis of retrograde menstruation with possible incubation of endometrial implants in the ovary is sufficiently familiar not to require much elaboration. In operations performed during the menses, blood has frequently been seen coming from the tubes and in several instances of atresia of the cervix a similar phenomenon has been observed. However, the grafting in the pelvis of devitalized endometrial elements found in menstrual blood is speculative and this hypothesis does not explain endometriosis of the groin or of the umbilicus.

King's assumption that hemorrhagic corpus luteum or other cysts of the ovary might be the starting point of endometriosis, relates the implantation with the metaplastic hypotheses and is subject to the same criticism.

Lymphatic metastasis.—This hypothesis assumes that endometrial tissue from the uterus may be carried by lymph channels to points outside the uterus. Sampson[18] suggested this possibility in 1922. Halban in 1924 was the first writer to put forward lymphogenous metastasis as a general explanation of all forms of endometriosis, which he called "metastatic hysteroadenosis." It is assumed that during menstruation, by virtue of the indefinite limit between endometrial tissue and the subjacent tissues, epithelial elements may enter open lymphatic vessels and be carried to the subserosal lymphatics or to the uterosacral ligaments, the broad ligament, the ovaries, the round ligaments or the abdominal wall. The known lymphatic drainage of the uterus enables the tracing of a possible course to all of the locations in which endometriosis has been described, including its occurrence in ordinary laparotomy scars. This hypothesis seems to explain the histopathologic phenomena in endometriosis more adequately than any other, since it assumes an origin from the uterus; it includes intrauterine adenomyomas as well as extrauterine endometriomas; it is consistent with the finding of endometrial tissue definitely within lymph nodes and within lymph capillaries (Gricouroff[4, 5] and Henry). The chief objection which one may raise to it is that normal tissue supposedly does not metastasize. However, Ewing pointed out that metastasis is associated with thyroid adenoma, chondroma, leiomyoma, and normal chorionic tissue; it must be noted moreover that the proliferation of the uterine mucosa and its proliferation into the uterine musculature during menstruation are unique processes in the normal organism and might be compared to the conditions which obtain in carcinoma. Normal islands of endometrial tissue have also been observed in the pelvic lymph nodes lying next to carcinomatous tissue in cases of carcinoma of the uterus (Leidenius).

The hypothesis of lymphatic metastasis must also include occasional blood vascular metastasis. The observation of Sampson in 1927 of viable endometrium which had entered the sinuous veins of the uterus

during menstruation does not appear to have been verified and Jacobsen reported in 1933 that he had failed to effect the transplantation of endometrium through the blood vessels. However, endometriosis of the lung has been observed by Schwarz and it is difficult to explain this on any basis other than a blood vascular dissemination.

CLINICAL PHENOMENA

Pelvic pain, usually associated with the menstrual periods, is the single most important symptom which induces the patient with endometriosis to consult the physician. Disturbances in the amount or character of the menstrual flow are usually of secondary importance and are seldom of such significance as to constitute the patient's prime complaint. It is important certainly that some patients with this disease have pelvic pain and that some do not, at least to any appreciable degree. Also, why it manifests itself in the great majority of cases during the latter part of the third decade or early in the fourth decade is a problem. The absence of pain may be ascribed to the fact that it is the rule to designate large chocolate cysts of the ovaries with intimate attachment to the uterus, cul-de-sac and bowel as endometriosis, although it is frequently impossible to demonstrate any endometrial tissue in any of the tissues removed surgically. However, one encounters true endometriosis associated with pain in which one finds coexistent chocolate cysts of the ovary and therefore there are probably two different but closely related pathologic entities. Broders states without reservation that tarry cyst formation of the ovary and endometriosis are two different conditions pathologically, although they may or may not coexist in the same patient. The foregoing remarks, therefore, imply that the endometrial implant is productive of pain, whereas it is my observation that mere chocolate cyst formation is rarely painful. Most patients with the latter condition seek medical attention for menstrual disturbances and not because of dysmenorrhea. The character of the pain then in endometriosis should have certain features which should aid in diagnosing the location and the extent of the disease.

Those who have been interested in the type of pain produced by viscera, such as the gastrointestinal tract for example, have definitely established the fact that there are two types of pain produced by an intrinsic lesion of the stomach or bowel depending on its location and extent. As long as the lesion is confined to that portion of the bowel only, the pain is of a visceral or sympathetic type and has no localizing symptoms, but if the lesion becomes penetrating or involves any adjacent tissue by an inflammatory reaction, the pain becomes somatic or spinal sensory in type. The pain then becomes referred over the course and extent of the spinal sensory nerve which projects to a particular segment of the trunk and can be localized in that area. A good example of this is noted in acute appendicitis. The pain at the onset is a generalized epigastric distress which is a visceral pain, but the instant the inflammation involves the local peritoneum the distress

becomes severe and localized over the right lower quadrant as a somatic or spinal sensory pain and, therefore, the abdominal wall becomes tender in proportion to the involvement of the peritoneum. Rivers has expressed the opinion that the visceral pain is due to the resistance to contraction, because there is no pain, for example, in a dilated stomach or intestinal segment where the dilatation is of long duration, and that the same situation becomes true for the biliary system or the urinary tract.

It seems logical to assume that the pelvic viscera and adjacent peritoneum should portray the same visceral and somatic type of pain as do the other abdominal viscera. There are several reasons to believe this to be true. For example, the pain experienced from an acutely inflamed Fallopian tube is at first a pelvic distress associated with some uterine cramps but within a few hours, or as soon as the peritoneum of the tube becomes inflamed, the pain is localized to either side involved and there is tenderness over the adjacent abdominal wall. This localized pain is often mistaken for acute appendicitis. On the other hand there is no pain in a chronically distended tube, for example in a hydrosalpinx. There is no pain experienced in a slowly developing ovarian cyst even though it attains tremendous size, but if it becomes acutely distended with blood or twists on its pedicle, a movement which involves the peritoneum at its base, the pain becomes severe and at once local in its distribution.

The pain of primary dysmenorrhea is a pure visceral or sympathetic type of pain, since nothing is involved but the contracting uterine musculature and the pain is referred to as a uterine cramp. If there is any change in the duration or severity of this pain or if a dysmenorrhea is acquired when one did not previously exist to any noticeable degree and if it becomes progressive, this is presumptive evidence that endometrial tissue has invaded the uterine musculature, since it is subject to the same physiologic stimulus as the normally placed endometrium. The dysmenorrhea is a prolonged and more intense visceral pain. However, it has been observed that if the endometrium is outside of the uterus itself, the pain is more likely to be of a different character; for example, an endometrioma of the round ligament produces pain which is referred to the inguinal regions, and those endometriomas located under the broad ligament and along the ovarian ligament are referred to the groin and inner side of the thigh, a pain which is purely somatic in type. One patient in our series in whom the lesions were along the left pelvic wall and lateral surface of the sigmoid, experienced pain only in the left epigastrium. The only explanation is that the pain was referred up to the spinal sensory nerve supplying that portion of the parietal peritoneum. When the endometrial tissue involves the rectovaginal septum or the peritoneum of the rectosigmoid juncture of the colon the distress is often referred to the anal region, and when the mucous membrane of the rectum becomes attached to it there is a desire to defecate. Rectal emissions

also are painful. Similarly endometriosis involving the bladder wall resembles cystitis in its symptoms.

The development of these various lesions is a slow and progressive affair. Probably the process is initiated soon after the onset of menstruation, but it does not become of clinical importance until in the third or fourth decade when the lesions become sufficiently diffuse. We at the Mayo Clinic are convinced that in girls in the second and third decades at least, endometriosis is in many cases responsible for pelvic pain and prolonged dysmenorrhea, although the lesions are not firm enough to palpate either vaginally or rectally. In many instances the prolonged dysmenorrhea is probably due to endometrial tissue within the uterine musculature.

In this connection it is of interest that in a recent series of 92 patients from whom definite information was obtained regarding dysmenorrhea it was ascertained that the average age of onset of severe symptoms was 28.8 years, but the symptoms of some patients had begun during the second decade. The average age at operation was found to be 37.1 years. Furthermore, the average duration of symptoms prior to surgical treatment was 10.3 years, excluding 18 patients in whom the duration was less than one year.

TREATMENT

Since heterotopic endometrium is subject to the same physiologic stimulus from the ovary as the normally situated endometrium, it naturally follows that removal of both ovaries or their destruction by radium or roentgen ray would render all endometriomas inactive. This is, of course, desirable if the patient is near the climacterium, but unfortunately most cases of endometriosis occur during the most active reproductive period of life, that is in the third and fourth decades. The problem then is one of relief from pain and preservation of the menstrual or reproductive functions or both. However, too much emphasis should not be placed on the latter for we have found that 48.9 per cent of 131 married patients with this disease either had never been pregnant or had had only miscarriages. The absolute sterility was 32.1 per cent. In view of this evidence one should not endeavor to preserve the reproductive function in cases where this disease is diffuse, but to restrict such efforts to instances where the disease is unilateral or where there are relatively few implants on the peritoneum, and where the adnexa are freely movable. Further important evidence militating against preservation of the reproductive function may be inferred from our results following conservative surgery in these patients. In 55 cases in which pregnancy could have reasonably been expected, it actually did occur in only 7 patients, resulting in a total of 10 children.

Since the average period of time which elapses from the onset until the patient seeks relief is ten years, it is most likely that the disease has become too extensive for satisfactory conservative surgical treatment. Our efforts then should be directed to relief of pain without

complete castration, at least when the patient is less than thirty-seven years of age. However, there are some instances in patients under this age in which it is futile to attempt any procedure other than castration or if feasible a panhysterectomy.

We feel that patients in the third and fourth decades of life at least should be submitted to surgical treatment rather than to radium or roentgen therapy, because it is impossible to determine clinically whether complete cessation of function of the ovary is advisable. Furthermore, it is much wiser to know whether there is any other associated pathologic condition of the pelvic organs before submitting the patient to castration by radium or roentgen rays. The one exception to this rule may be a large adenomyoma of the rectovaginal septum which cannot be removed surgically without considerable risk of producing a rectal fistula.

The relief of dysmenorrhea due to endometriomas is a simple matter when these are confined to the uterine musculature. Since the pain from the uterus is purely a visceral pain it should be adequately relieved by a presacral neurectomy together with complete excision of all uterine endometriomas. Also, it is probable that in these particular instances where the disease is confined to the uterus, presacral neurectomy will postpone disability from pain arising from recurrences within the uterus, or the patient may reach the menopause before further treatment becomes urgent.

Obviously presacral neurectomy is futile for the relief of pain arising from endometriomas involving the round ligaments, lateral pelvic walls, and so forth, a pain which is principally somatic in type. Therefore, in instances where the uterus itself is not involved, presacral neurectomy as a protection against recurring pain is hardly advisable.

Surgical treatment of heterotopic endometriomas other than those in the uterus should be influenced by the fact that in some instances almost complete relief has been obtained by cauterization of the implants or by partial resection by the surgical diathermy loop.

At the Mayo Clinic our surgical treatment consists in preservation of one or both adnexa where possible, and complete excision of all adenomatous tissue involving the uterus; in these patients a presacral neurectomy is routinely performed. Also, complete or partial excision of all heterotopic endometriomas is done with the surgical diathermy wire loop.

If the disease does not lend itself to these conservative procedures, then radical removal of all pelvic organs is performed regardless of the age of the patient.

SUMMARY

The various hypotheses regarding the etiology of endometriosis have been briefly outlined. From the manner of the distribution of the implants, the hypothesis that endometrial tissue from the uterus is carried by lymph channels to points outside the uterus presents the least objections to its explanation. The hypothesis is extremely simple, logical and entirely possible.

Pelvic pain, quite definitely related to menstruation, is the principal reason the patient seeks relief. There is usually a ten-year history from the onset of the disease and the symptoms have been progressive. There are most likely two types of pain, visceral or sympathetic and somatic or spinal sensory. The latter becomes evident when the peritoneum of the cul-de-sac, lateral pelvic wall, and round ligaments is involved.

Surgical treatment is either radical or conservative, depending on the extent and involvement of the lesions. If conservative treatment is performed it is necessary to carry out such procedures as will relieve pain as well as conserve the menstrual or reproductive functions. The pain may be relieved or alleviated by complete excision of the lesions from the myometrium plus a presacral neurectomy when the lesions are limited to the uterus. Other heterotopic lesions may be attacked by complete excision where possible by the surgical loop diathermy or partial resection when lesions are located in the sigmoid or the rectovaginal septum.

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DISCUSSION

DR. JAMES W. McGILL, Superior, Wis.—One of the etiologic possibilities not mentioned is that of disturbed ovarian function. Dougal of Manchester, for example, believes that the excessive production of estrin has a profound influence in the causation of endometriosis. Meigs of Boston has made the suggestion that late marriage, contraception, and late conception may be factors on the basis of continued stimulation by the follicular hormone, unrelieved by the physiologic rest, so to speak, furnished by the occasional advent of pregnancy.

The association of sterility with this condition is well recognized, although opinions differ as to the mechanism. Endometriosis is so frequently associated with ovarian or uterine disease that it is difficult to say which is the cause and which the effect. Sterility may be due directly to endometriosis or it may be due to ovarian dysfunction.

Even though conservative surgery is frequently disappointing inasmuch as subsequent operation is so often necessary, still one would hesitate to advise more radical treatment, especially in younger women. Yet Pemberton states categorically that the grounds for conservative treatment must be strong and clear to justify it.

If a patient is near the menopause it should be borne in mind that the condition will frequently subside without treatment. Because of the infiltrative character of the disease, radium must be used with caution. Severe necrosis may follow the use of intrauterine radium in the event that bowel is adherent to the uterus. The mere presence of endometriosis in itself does not justify treatment, in the opinion of Keene and Kimbrough; they believe that unless symptoms directly referable to the lesions are present, no treatment is indicated.

DR. WILLARD R. COOKE, GALVESTON, TEX.—For some time I have been making a study of the localization of pain in the pelvic region. For this study endometriosis has proved to be an excellent guide on account of its localization in various areas.

It is possible to differentiate between visceral and peritoneal pain. Peritoneal pain is referred to definite locations which do not correspond with the location of the various visceral types of pain. This observation has been so constant that we have been able to make diagnoses of endometriosis solely upon the peritoneal localization.

To aid in the diagnosis we ask the patient whether she has a new type of pain accompanying and following menstruation which is different from some previous type of dysmenorrhea and which has become more severe and more prolonged with each successive bleeding phase. If she gives a history of a different type of pain in a different location it is highly probable that she has developed an endometriosis.

In cases of endometriosis in younger women, it is of course undesirable to halt its progress by castration or other radical operative means, but at the same time these cases demand relief of pain. Presacral sympathectomy relieves pain only in the uterus, tubes, and to a limited extent in the upper vagina and the anterior wall of the cul-de-sac. It does not relieve pain due to endometriosis of the ovaries or of the intestinal tract. In cases of ovarian endometriosis we have found it necessary to divide the ovarian nerves which accompany the ovarian leash of vessels. Since it is impracticable to perform a periarterial sympathectomy, it is necessary to divide the ovarian arteries and veins, ligating each cut end. We have found this entirely satisfactory in relief of ovarian pain and without any sequelae in the form of disturbances of ovarian function. When the endometriosis is localized to areas of the peritoneum which are not innervated through the presacral plexus, but through spinal nerves, we have not found it possible to perform the necessary neurectomy.

We have had four cases in which neurectomy was performed and the endometriosis has undergone marked regression. One of these patients has had two children since the operation and there is no palpable mass. In another case the mass is reduced to a fifth of its original size; another has only a small mass in the right uterosacral ligament about the size of a pea. This case had practically a complete diffuse infiltration of the entire area between the genitalia and the anterior surface of the rectum.

From these cases it seems probable that regression and ultimate disappearance of the endometriosis may occur. Whether the sympathectomy and ovarian neurectomy had anything to do with the regression is problematic.

DR. JEAN PAUL PRATT, DETROIT, MICH.—It seems possible to relieve some of the pain due to endometriosis by cutting down the ovarian function. The pain of endometriosis is not constant throughout the cycle but occurs during the time that the endometrium is stimulated by the ovarian factor. If we cut down the amount of ovarian tissue it tends to reduce the amount of discomfort the patient experiences. We have found it quite helpful in reducing ovarian function to remove one ovary and a half or a third of the other. In instances in which this has been done, one patient has had three subsequent pregnancies which made the conservative procedure worthwhile. The majority are completely relieved of pain. They are told that if the pain returns, they can be entirely relieved by x-ray treatment of the remaining ovary. This has seldom been necessary because cutting down the ovarian function has made the patient reasonably comfortable.

DR. COUNSELLER (closing).—I believe the condition is closely allied to malignant disease and yet the tissue is supposed to be normal. Nevertheless, at the meeting of the American Gynecological Association, in Asheville, Dr. Schwarz, of St. Louis, referred to two cases of endometriosis of the lung in which the patients bled from the bronchus every month. A piece of tissue was removed through the bronchoscope; biopsy showed that it was ectopic endometrial tissue; therefore, roentgenotherapy was employed and the bleeding stopped.

My chief purpose in discussing this subject was to demonstrate that on the basis of the clinical signs one could tell the patient definitely regarding her chances of cure and whether radical operation would be required. If one could place on a chart where the pain is referred one could show that structures other than the uterus are involved. The prognosis as to subsequent pregnancy or recurrence could be more definite.

I have a slide showing a section of endometrium taken from the uterus of a woman twenty-two years of age. She was scheduled for hysterectomy. I excised either eleven or thirteen points of endometriosis, reconstructed the uterus and did a presacral resection. Since the operation she has been menstruating regularly and without pain. That was five years ago.

URETERAL INJURIES IN GYNECOLOGIC SURGERY*

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INJURY to the ureter is a serious complication in gynecologic surgery. It has been estimated from reports by several authors that 1 to 3 per cent of all pelvic operations are complicated by this accident. Although this incidence is very high according to our experience, there are undoubtedly many unrecognized and undiagnosed cases; particularly where complete ligation of a ureter leads to an aseptic atrophy of the involved kidney. In such cases, the remaining kidney takes up the complete urinary function without any symptoms or signs.

The type of injury is often difficult to determine unless recognized at the time of operation; but the various possibilities include ligation, transfixation by suture, angulation or constriction by adjacent ligation, incision (longitudinal, transverse) and necrosis. The latter may be due to pressure from a clamp or to circulatory disturbance following denudation, as not infrequently occurs in the extensive dissection involved in a radical Wertheim operation.

A realization on the part of the gynecologic surgeon of the course of the ureters normally and as modified by extensive pelvic pathology constitutes the best prophylaxis against ureteral injury. Brown, in his report of a group of postoperative ureteral injuries, states that normally the ureter is 1.5 cm. from the uterus at the internal os and 1.0 cm. from the cervix at the vaginal reflection. Such close proximity warrants the utmost caution in the placing of clamps and ligatures.

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., Oct. 6 to 8, 1938.

Since the course of the ureters may be markedly distorted in pelvic disease, the axiom "stick close to the pathology" is a good prophylactic measure in any complicated pelvic dissection. Incomplete mobilization of the bladder from the cervix invites catastrophe by placing the ureters too close to the field of clamp and ligature. This is especially pertinent in bladder plastics and hysterectomy, particularly total. Inclusion of the pubocervical fascia in the lower clamps during the performance of a total hysterectomy, as described by Richardson, diminishes the possibility of injury to the ureters. This technique also obviates unnecessary hemorrhage, where frantic attempts at hemostasis often lead to involvement of the ureter. An intraligamentous tumor usually causes marked distortion in the course of the ureter, and the control of bleeding from the bed of such a growth may endanger the ureteral integrity. In our experience we have found that troublesome bleeding in such a case is best treated by packing, drainage through the vagina and the construction of a "pelvic diaphragm," rather than by uncertain ligature. The value of inserting ureteral catheters as a prophylactic measure is highly questionable. They may give a false sense of security, and by altering the normal position of the ureters, render them more liable to injury. In many instances we have been unable to locate them by palpation, and their mere introduction may give rise to infection, ureteral colic, and oliguria, with great possibilities of increasing the postoperative morbidity.

In April, 1938, Feiner reported 8 cases of ureteral injury and collected 702 cases through 1936. Of the total of 710 cases, 109 were bilateral and 601 were unilateral. In 236 of these cases collected during the period 1925 to 1936, 23 per cent occurred during radical abdominal hysterectomy for cancer, 20 per cent during total abdominal hysterectomy for benign disease, 18 per cent during supracervical hysterectomy, 15 per cent during vaginal hysterectomy (one-third of these cases were radical Schuata operations for carcinoma), 10 per cent during salpingo-oophorectomy, and 8 per cent during procedures which included extraperitoneal cesarean section, forceps delivery, and anterior colporrhaphy. Since, in recent years, radiation therapy has replaced radical surgery in the treatment of carcinoma of the cervix, the largest etiologic group in ureteral damage should be eliminated.

In the fifteen-year period preceding July 1, 1938, there were 13 patients on the Gynecologic Service at the Michael Reese Hospital who sustained ureteral injuries. The larger proportion of these cases occurred after 1930, when the staff began to perform total hysterectomy more often for conditions which previously were treated by supravaginal hysterectomy. In addition to these cases, our report includes a patient upon whom a supravaginal hysterectomy was performed elsewhere, and who entered our service complaining of urinary incontinence. A diagnosis of right ureterocervical fistula was made, and nephrectomy was performed as the treatment of choice. Of the 14 patients, 12 sustained unilateral injury and 2 bilateral. The indications for surgery in the 14 cases were as follows: fibromyomas in 8 cases, cystocele in 4 cases, intraligamentous cysts in 2 cases (one of these was in association with multiple fibroids), and carcinoma of the

cervix in 1 case. All of the patients with cystocele were operated upon by the usual technique for anterior colporrhaphy. Of the 8 patients with fibroids, 6 had total hysterectomy. Of these, 2 had additional bilateral salpingo-oophorectomy and 3 unilateral salpingo-oophorectomy. The 2 remaining patients with fibroids were operated upon by supravaginal hysterectomy. In the patient with carcinoma of the cervix (Group II), a radical Wertheim operation was done (see Table I).

CASE REPORTS

CASE 1.—(E35478.) Mrs. M. L., aged 39 years, was admitted on March 6, 1931 with cystocele and rectocele. On March 9 an anterior colporrhaphy and perineorrhaphy were performed. The postoperative course was uneventful except for a continuous complaint of pain on the left side. The patient was discharged on the eighteenth day. On the following day she noticed incontinence and re-entered the



Fig. 1.—(Case 2.) Intravenous urogram six and one-half years after postoperative left ureterovaginal fistula. No treatment. Left hydronephritic atrophy.

hospital. The bladder dye test was negative for vesicovaginal fistula. On April 2, an intravenous pyelogram showed diminished kidney function on the left with distortion of the left renal pelvis. A diagnosis of left ureterovaginal fistula was made. The patient left the clinic and entered another hospital where on July 24, the left ureter was implanted into the bladder. On August 2, she developed a large mass in the left renal region, and on August 8, a decapsulation and nephrostomy were done. The patient left the hospital on October 19. There was no follow-up.

CASE 2.—(B49421.) Mrs. Y. T. was admitted on Dec. 24, 1931 with cystocele and rectocele. On December 28, an anterior colporrhaphy and perineorrhaphy were performed. The postoperative course was marked by temperature rise up to 101° F. for sixteen days with gradual subsidence to normal. Involuntary urination was noted from the fifth to the ninth days but none thereafter. The patient was discharged on the twenty-fourth day feeling well. Ten days later she had involuntary urination and re-entered the hospital. After the usual tests a diagnosis of vesicovaginal and left ureterovaginal fistulas was made. On March 31 the vesicovaginal fistula was successfully repaired. On the eleventh postoperative day an intravenous pyelogram showed a marked left hydronephrosis. Nephrectomy was advised but the patient refused and left the clinic. She returned on Aug. 15, 1938, feeling well. The leakage had cleared up after one year. Intravenous pyelogram on this date

showed a normal right kidney and ureter and a large nonfunctioning left kidney (hydronephrotic atrophy). Cystoscopic examination revealed a complete blockage of the left ureter 1 cm. from the ureteral orifice (Fig. 1).

CASE 3.—(B76048.) Mrs. A. F., aged 46 years, entered the hospital Sept. 20, 1932 with a moderately severe diabetes and a large cyst filling the right half of the pelvis. She had had a previous supravaginal hysterectomy and bilateral salpingectomy. On Sept. 24, 1932, a laparotomy was performed at which time a right intraligamentous cyst 15 cm. in diameter and an adherent appendix were removed. The pathologist reported 8 cm. of ureter adherent to the removed cyst. The postoperative course was marked by daily temperatures of 101° to 102° F. On the fifth day, a large tender mass was noted which filled the right abdomen. An intravenous pyelogram on Oct. 8, 1932 showed a large right kidney with a considerable grade of hydronephrosis, and a dilated right ureter which appeared to end in a rounded shadow the size of a football (Fig. 2). On October 13, 1932 an incision was made over the right kidney region and about a liter of urine was evacuated. The ureter was ligated about 10 cm. below the kidney pelvis and drainage instituted. The patient was discharged on Nov. 8, 1932 with a urinary fistula at the flank. On May 8, 1934 her condition was much improved and a nephrectomy was performed. She had an uneventful postoperative course, and left the hospital on the fourteenth postoperative day in good condition.

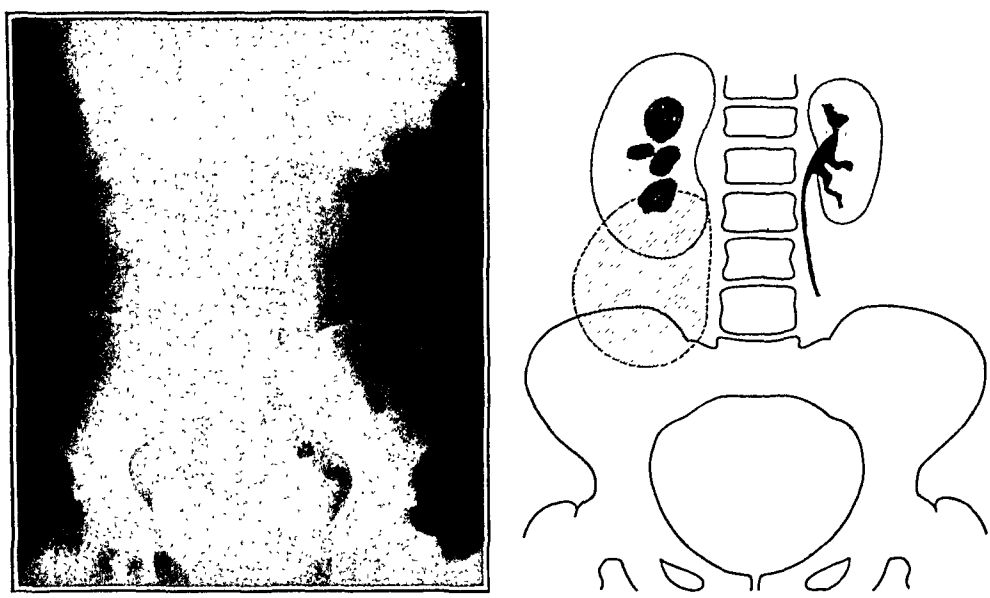


Fig. 2.—(Case 3.) Intravenous urogram fourteen days postoperative. Complete resection of right ureter with hydronephrosis and extraperitoneal extravasation of urine. Nephrectomy.

CASE 4.—(B6318.) Mrs. M. K., aged 44 years, entered the hospital May 8, 1933 with a complaint of incontinence. On March 9, 1933, she had had an operation for uterine fibroids performed at another hospital and twelve days postoperatively she began to lose urine through the vagina and developed pain in the right lumbar region. Examination showed urine coming from the cervical os and the bladder dye test was negative for vesicovaginal fistula. Intravenous pyelography showed right hydronephrosis. A diagnosis of ureterocervical fistula was made and on May 12 a right nephrectomy was performed. The postoperative course was normal and the patient left the hospital on May 23 in good condition.

CASE 5.—(C5111.) Mrs. B. H., aged 43 years, entered the hospital on Aug. 21, 1935 with a diagnosis of early carcinoma of the cervix (Group II). On August 26 a Wertheim panhysterectomy was performed, using the high-frequency cutting current. The postoperative course was marked by a moderate elevation in temperature for forty days. Involuntary urination began on the third postoperative day. The

bladder dye test was negative for vesicovaginal fistula, and she was notified to return for future nephrectomy after regaining strength. On April 3 an intravenous pyelogram revealed tremendous dilatation of the right renal pelvis and ureter, and on April 9, a right nephrectomy was performed. The patient left the hospital in good condition on the ninth postoperative day.

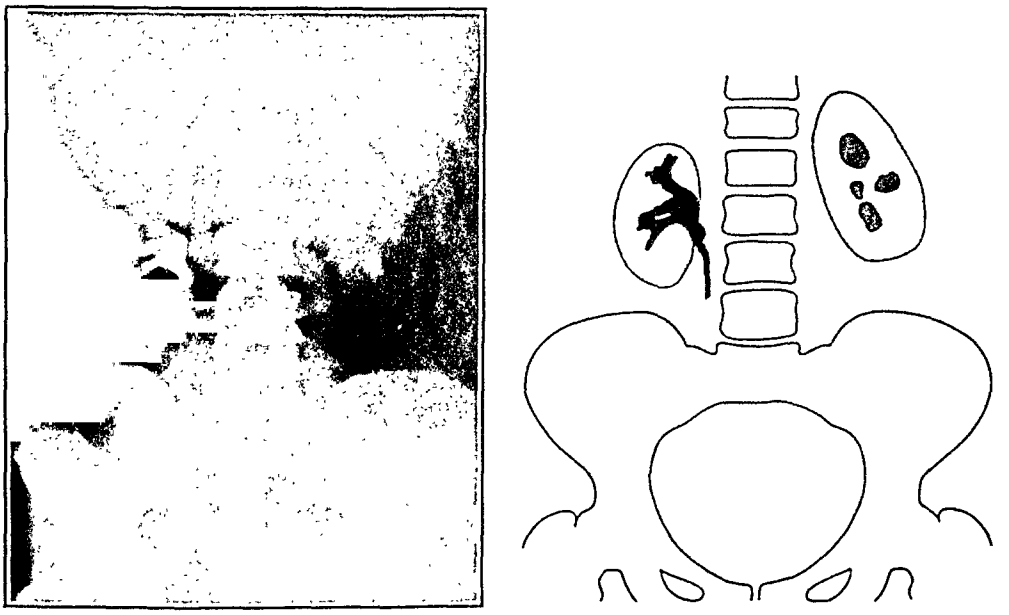


Fig. 3.—(Case 6.) Intravenous urogram one month following total hysterectomy. Left ureterovaginal fistula of seven days' duration. Left hydronephrosis. Treatment by indwelling ureteral catheter.

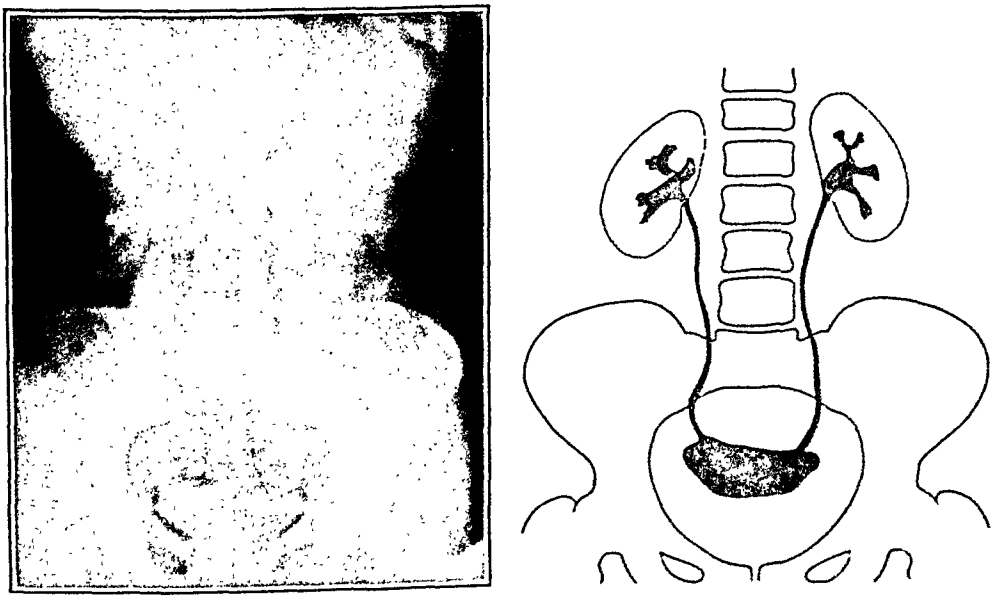


Fig. 4.—(Case 6.) Two years after treatment by indwelling ureteral catheter. Fistula healed. Normal kidney status.

CASE 6.—(C10629.) Mrs. M. H. was admitted on July 20, 1936, and on July 23 a total hysterectomy and bilateral salpingo-oophorectomy were performed for multiple fibroids including one that was intraligamentous. The postoperative course was normal except for a slight rise in temperature and a complaint of pain in the back on the fifth postoperative day. The patient was discharged from the hospital feeling well on August 6, and on August 18 was readmitted with pain in the left lower quadrant and constant leakage of urine from the vagina for the past four

days. The bladder dye test was negative for vesicovaginal fistula. On August 21 an intravenous pyelogram showed a left hydronephrosis (Fig. 3). On cystoscopy, a ureteral catheter was passed beyond the stricture with difficulty and left in situ. The catheter was changed on August 25 and 29. No vaginal drainage of urine was noted after August 21. On September 1, the catheter was removed. On September 9, an intravenous pyelogram revealed practically a normal renal pelvis. The patient was discharged from the hospital September 30 with normal urinary function. On Aug. 25, 1938 (two years later) an intravenous pyelogram revealed normal kidney outline and function bilaterally (Fig. 4).

CASE 7.—(B75956.) Mrs. K. J., aged 32 years, entered the hospital on April 28, 1934 with a diagnosis of fibromyomata uteri. On May 1, 1934, a total hysterectomy was performed. The patient had a normal postoperative course except for pain in the left lumbar region on the tenth day, and on the thirteenth day urine appeared in the vagina. The bladder dye test was negative for vesicovaginal fistula. On the twenty-first day cystoscopic examination revealed slight edema of the left ureteral orifice. On the forty-fourth day an intravenous pyelogram showed marked left hydronephrosis and hydro-ureter. The patient was discharged on the sixty-second day still draining urine from the vagina. There was no follow-up.

CASE 8.—(B88727.) Mrs. R. K., aged 48 years, entered the hospital on Jan. 25, 1935 with a diagnosis of fibroid uterus and cystocele. On January 29 a vaginal hysterectomy and anterior and posterior plastic were done. The postoperative course was normal except for pain in the lower left quadrant. She was discharged from the hospital on the nineteenth postoperative day feeling well, and was readmitted to the hospital March 19, 1935 (forty-nine days postoperative) because of a constant leakage of urine from the vagina since the day of discharge from the hospital. Cystoscopy and ureteral catheterization revealed obstruction in the left ureter 0.5 cm. from the bladder. An intravenous pyelogram on March 19 showed diminished filling of the left renal pelvis with marked hydronephrosis and hydro-ureter down to the ureterovesical junction. On March 25, 1935 an extraperitoneal transplantation of the left ureter into the bladder was performed and a ureteral catheter was passed into the bladder through a fresh incision in the ureter and sutured to the skin. The catheter was removed on the eighteenth postoperative day and the incision healed promptly. The patient was discharged feeling well four days later. On May 6, 1935 the abdominal wound reopened with constant drainage of urine producing a ureteroabdominal fistula. On June 14, 1935 a left nephrectomy was done at another hospital and the patient made an uneventful recovery.

CASE 9.—(C19764.) Mrs. R. P., aged 32 years, entered the hospital Feb. 2, 1937, with a diagnosis of multiple fibroids including cervical fibroids and pregnancy. On Feb. 3, 1937 a total hysterectomy and left salpingo-oophorectomy were performed. There was complete anuria for forty-eight hours. On February 5, cystoscopic examination revealed bilateral ureteral block about 3 cm. above the vesical orifices. Nonprotein nitrogen was 74. On February 9 the dome of the vagina was opened with dressing forceps, about 300 c.c. of urine was obtained and drainage was instituted. On Feb. 11, 1937, the nonprotein nitrogen was 280 and the creatinine 6, despite a urinary output of approximately 150 ounces in twenty-four hours. On February 12, the patient died. Autopsy revealed bilateral occlusion of the ureters by ligation, with ascending pyelonephritis and hydro-ureters.

CASE 10.—(C23242.) Mrs. D. A., aged 38 years, was admitted on April 18, 1937, and on April 19 a total hysterectomy and right salpingo-oophorectomy were performed for multiple uterine fibroids including cervical and intraligamentous fibroids. On the following day only two ounces of blood tinged urine were obtained, but some urine leaked through the vagina. On April 21, the nonprotein nitrogen was 58 and all the urine passed through the vagina; none through the catheter. On April 26, an intravenous pyelogram showed bilateral dilatation of the renal pelves and ureters down to the iliopectineal lines. On cystoscopy the passage of ureteral catheters was impossible because of the markedly edematous bladder wall. A left nephrostomy was done, but only a small amount of urine drained during the next

twenty-four hours. The patient died on April 28 and autopsy was refused. Clinically, the patient showed definite evidences of peritonitis.

CASE 11.—(C30043.) Mrs. A. S., aged 35 years, entered the hospital Aug. 25, 1937 with a diagnosis of uterine fibroids and left ovarian cyst. She gave the history of having a double uterus with two pregnancies, both on the right side. On August 27, a total hysterectomy and left salpingo-oophorectomy were performed. The postoperative course was uneventful until the eleventh day when urine was noted in the vagina. The bladder dye test was negative for vesicovaginal fistula. During cystoscopy on the eighteenth day, it was impossible to pass a catheter through the left ureteral orifice because of marked edema of the bladder mucosa. Intravenous pyelography revealed a normal right side. The left side showed delayed concentration. The superior calyx was club-shaped and connected to a ureter which crossed the main ureteropelvic junction and took a lateral course. The medial and inferior calyces were markedly dilated and connected to a main pelvis which in turn entered a tremendously dilated ureter which was medial to the above ureter (hydro- and pyelonephrosis in a congenitally double ureter and pelvis as a result of pelvic obstruction) (Fig. 5). A left nephrectomy was performed on the twenty-sixth postoperative day and the patient made an uneventful recovery.

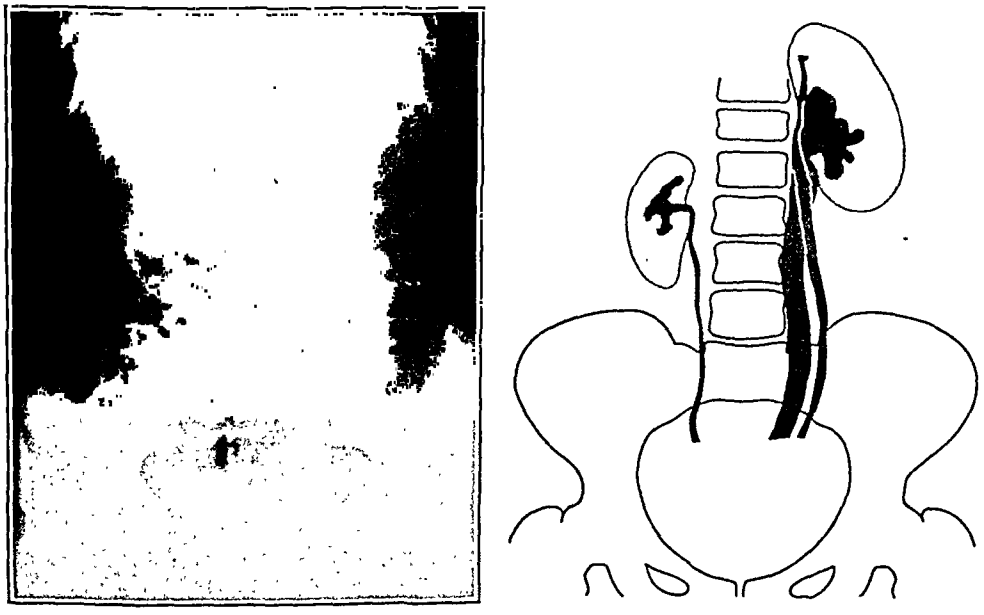


Fig. 5.—(Case 11.) Intravenous urogram eighteen days after total hysterectomy of uterus didelphys with fibroid. Left ureterovaginal fistula of one of double ureters, with hydronephrosis and pyelonephrosis of medial and inferior calices. Nephrectomy.

CASE 12.—(C36730.) Mrs. V. E., aged 30 years, entered the hospital on Jan. 12, 1938, with a diagnosis of fibromyomata uteri. At operation a large right tuboovarian abscess was found in addition to the fibroids. After removing the abscess and performing a total hysterectomy and bilateral oophorectomy, the right ureter was discovered to be divided. The distal end was ligated with silk and the proximal end implanted into the mobile sigmoid by a modified Coffey technique. The postoperative course was febrile and marked by a wound infection. However, after the third postoperative day, the patient began to pass urine per rectum. On Feb. 15, 1938, an intravenous pyelogram revealed diminished concentration in the right pelvis with dilated calyces. The patient was discharged on February 18 feeling well. On March 17, 1938 an intravenous pyelogram showed relatively little dilatation of the pelvis and calyces. The patient appeared in good health and the only complaint was frequent watery stools. On May 5, 1938, excretion urography showed delayed concentration but in thirty minutes the outline of the right urinary tract could be made out. There was relatively little dilatation of the pelvic calyces, although the latter were blunt.

CASE 13.—(B82697.) Mrs. A. C. entered the hospital Aug. 10, 1933 with a large cystocele and uterine prolapse. On August 11, an anterior and posterior vaginal plastic were done. The postoperative course was uneventful and the patient was discharged on the twelfth postoperative day. After being home a few days the patient noted loss of urine from the vagina and pain in the left flank. An intravenous pyelogram on Sept. 5, 1933 showed no renal pathology. At various times after this, attempts were made to catheterize the ureters. The right was normal, but the left could not be catheterized for more than 1 cm. A diagnosis of left ureterovaginal fistula was made. On Oct. 6, 1934 the left ureter was transplanted into the bladder above the site of the fistula and a permanent bladder catheter inserted. The patient made an uneventful recovery, and there was a complete cure of the fistula. On Sept. 15, 1938 intravenous urography showed a normal urinary status (Fig. 6).

CASE 14.—(C18098.) Mrs. M. L., aged 48 years, entered the hospital on Dec. 12, 1936 with the diagnosis of cystocele and rectocele. On December 28, anterior colporrhaphy and perineorrhaphy were done. During the first five postoperative days

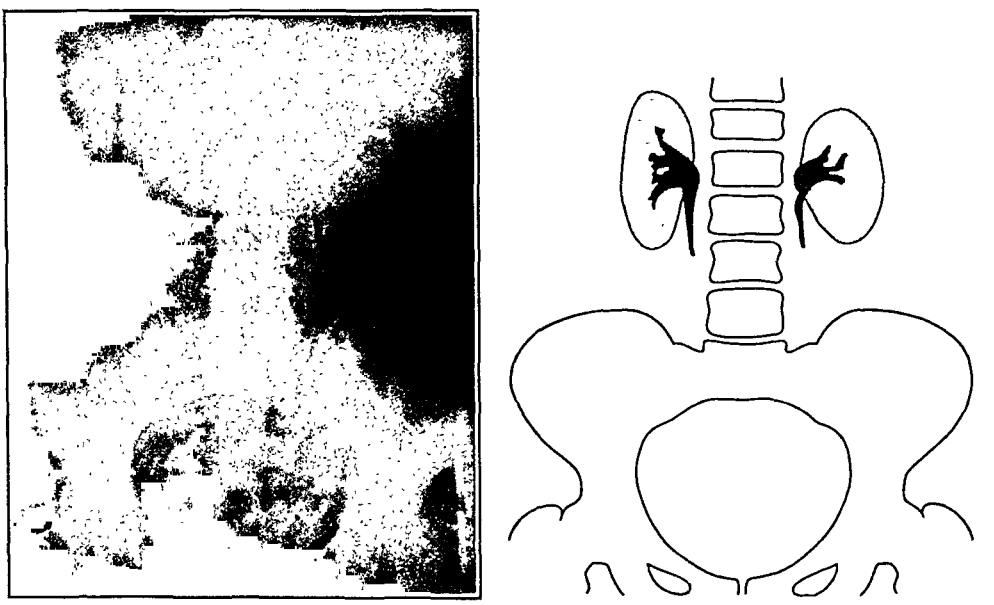


Fig. 6.—(Case 13.) Intravenous urogram four years following left ureterocystostomy for ureterovaginal fistula. Original operation anterior colporrhaphy. Normal kidney status.

the patient had chills and fever. The temperature ranged from 103 to 106° F. and there were 18 to 24 ounces of urine excreted daily. On the seventh postoperative day, cystoscopy revealed an edematous and inflamed bladder floor. The right ureter could not be catheterized because of edema. Nonprotein nitrogen was 152. Indigo carmine intravenously on January 5 showed no trace of urine or dye from the right ureter. The patient died on January 6. Autopsy revealed ligation of the right ureter with right hydro-ureter, right ascending pyelonephritis with multiple abscesses, confluent bronchopneumonia, and acute fibrinous pleuritis.

The diagnosis of ureteral injury must be made as early as possible in order to institute effective therapy. This is especially true for the bilateral cases where immediate recognition is essential in order to preserve life. Fortunately, it is easy to diagnose bilateral ligation of the ureters as there is always an anuria following the operative procedure. In order to be sure that the ureters have sustained no injury, bladder catheterization is essential at the end of any operation in which the ureters might possibly be injured. If no urine is obtained

after the initial immediate postoperative catheterization, treatment for bilateral occlusion of the ureters must be instituted at once. It must be remembered, however, that total anuria may follow a unilateral ligation. This is due to a renorenal reflex similar to that which occurs in unilateral occlusion of the ureter by stone. This possibility may be ruled out by cystoscopy with ureteral catheterization. Retention of nitrogenous products in the blood occurs in bilateral obstruction of the ureters, but to wait for a rising nonprotein nitrogen before instituting treatment may invite disaster. Intravenous urography is contraindicated in cases of anuria from any cause, as there is no secretion by the kidneys, and hence no visualization. Furthermore, the retention of a large quantity of iodine in the blood stream may be detrimental to the patient.

In unilateral injury to the ureter, the diagnosis may be much more difficult. The symptoms may vary from none at all to complete reflex anuria. If a complete division of the ureter occurs, the first sign may be the accumulation of fluid in the abdomen or retroperitoneally. If the urine is sterile, there may be pain without any toxic symptoms, but when infection supervenes, the course is marked by chills and fever. The establishment of drainage via the flank is important in such cases.

The occurrence of ureterovaginal fistula may be almost immediate or delayed for days or weeks. In our series of cases the earliest time for the appearance of urine in the vagina was the fourth postoperative day and the latest time the thirty-fourth postoperative day, the average being the seventeenth day. The late cases are due to slow necrosis rather than to incision of the ureters. Cystoscopy and ureteral catheterization should be carried out as soon as the possibility of a ureteral injury is suspected. An empty bladder with bilateral obstruction definitely establishes bilateral occlusion. One must be cautious in the interpretation of impassable obstruction, as not infrequently the ureter is tortuous, especially following a gynecologic operation. In such cases, retrograde pyelography will readily clarify a doubtful diagnosis. Cystoscopy will also differentiate a vesicovaginal from a ureterovaginal fistula. Intravenous urography is an invaluable procedure in the diagnosis of unilateral injuries without anuria. In complete unilateral ligation there will be a total inhibition of function on the affected side. In division of the ureter with urine accumulations, the latter are distinctly visible (Case 3); and after a ureterovaginal fistula has formed, the resultant hydronephrosis becomes apparent. Repeated intravenous urograms aid in determining the efficiency of such treatments as uretero-ureterostomy, ureterocystostomy, and uretero-enterostomy.

The prognosis for the patient following ureteral injury is dependent upon early recognition (preferably at the time of operation), proper treatment, and the skill of the gynecologist and consultant urologist.

The treatment of ureteral injury is highly individualized and depends upon the condition of the patient, the time of discovery, and

TABLE I. RÉSUMÉ OF FOURTEEN CASES OF POSTOPERATIVE URETERAL FISTULA

CASE NO.	GYNECOLOGIC		URETERAL FISTULA				
	DIAGNOSIS	OPERATION	TYPE*	SIDE	URINE IN VAGINA	TREATMENT	RESULTS
1	Cystocele	Anterior colporrhaphy	U-V	L	19th day	Ureterocystostomy Nephrostomy	Fistula healed No follow-up
2	Cystocele	Anterior colporrhaphy	U-V	L	34th day	Refused Nephrectomy advised	Hydronephrotic atrophy Fistula healed. Cure
3	Right intraligamentous cyst	Right oophorectomy	U-A	R	—	Nephrectomy	Cure
4	Fibroid uterus	Supra-vaginal hysterectomy	U-C	R	12th day	Nephrectomy	Cure
5	Cancer of cervix	Wertheim	U-V	R	4th day	Nephrectomy	Cure
6	Fibroid uterus	Total hysterectomy Bilateral salpingo-oophorectomy	U-V	L	24th day	Ureteral catheter	Cure
7	Fibroid uterus	Total hysterectomy	U-V	L	13th day	Expectant	No follow-up
8	Fibroid uterus	Vaginal hysterectomy	U-V	L	20th day	Ureterocystostomy Nephrectomy	Cure
9	Cervical fibroid pregnancy	Total hysterectomy Left salpingo-oophorectomy	U-V	Bilat.	4th day	Expectant	Died
10	Fibroid uterus	Total hysterectomy Right salpingo-oophorectomy	U-V	Bilat.	2nd day	Left nephrostomy (late)	Died
11	Fibroid uterus didelphys	Total hysterectomy Left salpingo-oophorectomy	U-V	L	11th day	Nephrectomy	Cure
12	Fibroid uterus. Right tuboovarian abscess	Total hysterectomy Bilateral salpingo-oophorectomy	Complete section	R	—	Right ureterosigmoidostomy (at operation)	Cure
13	Cystocele	Anterior colporrhaphy	U-V	L	20th day	Ureterocystostomy	Cure
14	Cystocele	Anterior colporrhaphy	Complete ligation	R	—	Expectant	Died (Urinary sepsis)

*U-V, ureterovaginal; U-C, ureterocervical; U-A, ureteroabdominal.

the type of damage. Injuries discovered at the time of operation may be treated in various ways. If the ureter is divided and the condition of the patient is precarious due to a prolonged operative procedure, it is probably best to perform ligation. This is usually followed by an aseptic atrophy of the involved kidney, and therefore one must be certain of the normal structure of the opposite kidney which may be determined by palpation. If the condition of the patient is favorable, an end-to-end anastomosis over a large indwelling catheter is the method of choice. The catheter should be passed into the bladder and brought out through the urethra. It is of utmost importance that the catheter drains freely postoperatively, as any obstruction would allow urinary seepage along its side with subsequent disruption of the line of suture. In order to obviate this, Curtis has advised deviation of the urinary stream above the line of suture. This is accomplished by means of a catheter placed into a ureteral slit which directs the urine from the kidney through a stab wound in the flank. The value of this method was demonstrated experimentally on dogs by Bump and Crowe. As an additional precaution, the site of anastomosis should be extraperitonized and drained. If the injury is close to the bladder, extraperitoneal implantation into that organ is the proper procedure. The bladder in the female is very mobile and can be brought quite high in the abdomen in order to effect such an anastomosis. However, one must guard against tension at the site of anastomosis. Ureterointestinal anastomosis is a dangerous and radical procedure, and we do not recommend its usage, in spite of the fact that it was employed successfully in one of our cases, where the injury occurred in the mid-ureter with considerable loss of ureteral length (Case 12). Instead, we would advise ureteral ligation, or, if the condition of the patient permits, immediate nephrectomy.

When the injury is discovered postoperatively, the treatment is based on the bilateral or unilateral nature of the injury. When bilateral occlusion of the ureters is recognized, there must be no delay in instituting treatment, as there can be no "watchful expectancy," and a pathway for the drainage of urine must be provided for at once. We are in favor of bilateral nephrostomy to provide this drainage. In support of this judgment are: (1) It can be done under local anesthesia with little or no shock using the technique of Rolnick; (2) the operation is technically simple and is carried out through normal structures; (3) if the patient's condition is precarious, it can be terminated after one side is completed with the knowledge that urine drainage from one side will suffice to save the life of the patient; and (4) it does not preclude the possibility of restoration of ureteral continuity at a later date either spontaneously by absorption of the occluding ligatures, or by a plastic operation when the patient is in good condition. Experimentally, Caulk and Fisher have shown that immediate nephrostomy would preserve kidney function and allow restoration of the lumen of the ureter. Caulk found that ligatures required

approximately three weeks for absorption and that the patency of the lumen of the ureter was established in six to eight weeks. It is his opinion that the catgut will never absorb before the death of the kidney. Rolnick has shown that nephrostomy causes very little permanent injury to the kidney. Deligation is not to be generally recommended as it involves an inhalation or spinal anesthesia, invasion of a freshly operated field in a sick patient, and the possibility of not finding the offending ligatures. Furthermore, even if the ureters are released, the resultant damage may be enough to produce necrosis with subsequent fistula formation. The bilateral ureteral damage in Case 9 of our series might have been advantageously treated by nephrostomy.

In cases of unilateral injury to the ureter recognized postoperatively, there is rarely any need for haste, and intervention may be delayed until there has been complete recovery from the original operation. Not infrequently, in spite of no treatment at all, there may be healing of the fistula with restoration of kidney function or healing by cicatrix with aseptic death of the involved kidney. The latter method was exemplified in Case 2. However, in the presence of an intra- or extraperitoneal accumulation of urine, drainage must be established and the proximal cut end of the ureter placed in the flank. This was done in Case 3 of our series, and the patient remained comfortable with a ureterocutaneous fistula after which nephrectomy was finally performed. When a ureterovaginal fistula is first discovered, every effort should be made to introduce a ureteral catheter toward the kidney past the site of the injury. In one of our patients (Case 6) this in itself proved sufficient to re-establish the continuity of the ureter, the fistula healing without stricture formation and with complete restoration of kidney structure and function (Figs. 3 and 4). While it is true that many fistulas will heal by utilization of this method, repeated intravenous urography should be carried out to make sure that the healing of the fistula is not followed by the death of the kidney. If a ureteral catheter cannot be introduced beyond the fistulous opening, and there is radiologic evidence of dilatation of the ureter and kidney with good kidney function, extraperitoneal reimplantation of the ureter into the bladder should be attempted (Cases

TABLE II. OUTLINE OF TREATMENT OF URETERAL INJURIES

(Listed in order of importance)

RECOGNIZED AT OPERATION	RECOGNIZED POSTOPERATIVELY
1. Ureteroureterostomy	Bilateral
2. Ureterocystostomy	1. Nephrostomy
3. Ureteroenterostomy	2. Deligation
4. Ureteral ligation (atrophy of kidney)	
	Unilateral
	1. Ureteral catheter
	2. Ureterocystostomy (extraperitoneal)
	3. Nephrostomy (palliative)
	4. Nephrectomy

1 and 13). Fig. 6 demonstrated a perfect end result of ureterocystostomy. In those cases in which infection has supervened and there is marked renal destruction, nephrectomy may prove to be the most conservative procedure. Table II shows in outline the procedures we advise in the treatment of ureteral injuries listed in order of their importance.

SUMMARY AND CONCLUSIONS

1. Fourteen cases of ureteral injury are presented and analyzed.

2. Ureterovaginal fistula is the most common sequela of ureteral injury in gynecologic surgery.

3. Total abdominal hysterectomy is responsible for the greatest number of ureteral injuries. In the series herein reported, anterior colporrhaphy for cystocele comprises the second largest group.

4. The mortality from bilateral ureteral injury is extremely high. Early nephrostomy may be a life-saving measure.

5. The treatment of unilateral injury of the ureter is fully discussed. Nephrectomy may be the most conservative treatment in many instances.

6. The result of treatment depends upon the time of discovery of the injury and the close cooperation of the gynecologist and consultant urologist.

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DISCUSSION

DR. JAMES C. MASSON, Rochester, Minn.—Dr. Leventhal mentioned the necessity of knowing the anatomic relations and positions of the ureters. This is important, but in the presence of pelvic disease it is often difficult to judge and I think the more important rule should be to know what structures are cut, clamped, or tied.

I am inclined to think that many ureters are injured as the result of an attempt to control unexpected hemorrhage in the base of the broad ligaments without first isolating the ureters. It is much better to let a little blood flow rather than to risk the clamping or ligating of a ureter.

According to the essayist's statistics, in 8 out of 14 cases in which the ureters were injured total abdominal hysterectomy was performed, and there were only two injuries following subtotal hysterectomy. Personally I have been under the impression for many years that there was no more danger of injuring the ureters or bladder if a careful technique was used in performing total than the subtotal operation.

In the case of benign conditions I tie the uterine vessels in exactly the same place whether I do the total or subtotal operation.

I would like to draw attention to the fact that, of the six cases of total abdominal hysterectomy in which fistulas developed in Dr. Leventhal's series, five had operations on the tubes and ovaries as well. I feel that there is a definite danger of the ureters being injured in closing the peritoneum on the side of the pelvis. The one and only case of injured ureter in this location that I have had in a great many years happened just about a year ago.

In cases of bilateral injury, an operation should be undertaken as soon as possible after ureteral catheterization confirms the diagnosis. If the patient is in good condition the cause of the obstruction should be removed and, if practical, transplantation of the ureters into the bladder should be done. If the condition of the patient will not allow this, drainage into the vagina should be established or nephrostomy should be carried out on both sides. It is more of an operation to transplant the ureters into the loin, and it is forever after impossible to connect them to the bladder. Only in cases of bilateral injury is it advisable to consider transplantation of the ureters into the sigmoid, if it is not practical to transplant them into the bladder, and this should only be done after the patient has completely recovered from the primary operation. I have had one case (about eight years ago) in which this was done following necrosis of both ureters about twenty-one days after a Wertheim hysterectomy. This patient has since married and about two years later I heard that she was still well.

In cases of unilateral injury, providing the other kidney and ureter are normal and it is impossible or impractical to re-establish the lumen of the ureter or to transplant it into the bladder, either ligation of the injured ureter or nephrectomy is indicated. If there is no infection, ligation alone preferably with silk is quite satisfactory.

In the years 1935, 1936 and 1937 at The Mayo Clinic, there were 1,080 total abdominal hysterectomies, 452 subtotal hysterectomies, 381 vaginal hysterectomies, and 640 primary operations on the tubes and ovaries, or a total of 2,553 cases. Besides the one case I referred to in which the ureter was injured on my service, there was one case of injury following a Wertheim operation. In both of these cases nephrectomy was performed and the patients are both alive and well.

DR. ARTHUR H. CURTIS, Chicago, Ill.—A feature ordinarily overlooked is that, after removal of the tube and ovary, the ureter lies very close beneath the ligated stump of the infundibulopelvic ligament, at the lateral wall of the pelvis. When burying the infundibulopelvic ligament stump, the first peritonizing suture must be placed with caution and not deeply; otherwise there is considerable danger of transfixing the ureter.

DR. RALPH LUIKART, Omaha, Neb.—Dr. John G. Clark stated that one should never tie vessels in the lower uterine segment unless the peritoneum has been turned out. You cannot catch the ureter if proper denudation of the peritoneum has been done. When there is a fibroid in the broad ligament or at the internal os, total hysterectomy should not be done, for that is the type of case which is likely to result in ligation of a ureter.

DR. LEVENTHAL (closing).—The large mortality with ureteral injury occurs in the bilateral cases. It is, therefore, necessary where injury of the ureter is suspected to catheterize the patient immediately after surgery to empty the bladder. If, after the initial catheterization, the bladder remains empty, then treatment must be instituted immediately. A pathway for the flow of urine must be established at once. Nephrostomy is the best treatment for this. It is a simple procedure and can be done very quickly and under local anesthesia. The field of operation is through normal structures rather than through previously operated structures. If the patient's condition is precarious, even in the bilateral cases, a unilateral nephrostomy may be done. According to some authorities it takes about three weeks for the catgut to absorb around the ureter if the ureter were completely ligated. If nephrostomy is done, the catgut may absorb and the continuity of the ureter be re-established in five or six weeks. That has been shown experimentally.

Drainage through the vagina with the establishment of a pelvic diaphragm does not produce a raw surface. It will not in our opinion lead to a dangerous obstruction of the small bowel, if, when the diaphragm is constructed, the sigmoid is sewed in a transverse direction to the reflected bladder peritoneum. We have done this in many instances following extensive pelvic dissection where peritonization was impossible.

THE CLINICAL SIGNIFICANCE OF APPENDICES EPIPLOICAE*

HOWARD C. WALSER, M.D., DETROIT, MICH.

THE appendices epiploicae are little fringes or bags of redundant peritoneum containing fat hanging from the free edge of the large intestine. They are found most often on the lower aspect of the transverse colon and inner border of the descending colon and sigmoid. If found on the ascending colon, they are located on the inner aspect. They are rarely seen in childhood but Oddono has shown that they appear in the fifth month of fetal life, first on the descending colon and sigmoid flexure. Piersol has seen them before birth also.

It is often stated that the appendices epiploicae occur along one of the bands or taeniae of the colon but this relation is at least not constant although they are generally arranged in a single line. They vary in size, usually being less than 2.5 cm. in length and less than 1 cm. in thickness at the free end. I have seen them as long as 7 cm. with a bulbous tip 2 cm. in thickness hanging by a much thinner pedicle. They may be overlooked in thin subjects but are usually more prominent in fat ones. They are easily found in persons who have been obese and lost weight for some reason, probably because in depleted states, intestinal fat is lost rather late in the progress of the decline.

Anatomically the epiploic appendix contains a central artery and vein which are small branches from the mesentery of the colon which have encircled the gut externally underneath the visceral peritoneum. The blood supply is minimal as in all fatty tissues and because of the length of the pedicle, twisting and strangulation of the appendix with resultant fat necrosis and gangrene must not be an uncommon condition.

The weight and pull of an epiploic appendix on the bowel itself possibly result in unpleasant sequelae at times. One author mentions this item as a possible cause or at least a predisposing factor in the development of diverticula of the colon. Certainly diverticula are more common on those parts of the colon where epiploic appendices are seen too. An atonic bowel must be a necessary condition present if this is to occur, as it is difficult to see how a small fatty appendage can cause sacculation from its weight alone if the bowel is healthy and strong. However, Da Costa reports that sacculation of the colon from such causes does occur and that perforation from a foreign body may take place in the sac, an epiploic abscess resulting which may attain considerable size and may be mistaken for carcinoma. Prob-

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

ably the most frequent end result of disturbance in circulation of an epiploic appendix is a necrosis of the pedicle which allows the appendage to become completely separated from the bowel. Maingot suggested that this is one of the uncommon conditions causing an acute abdomen, and that separation results in a natural cure. This leaves loose fibrofatty bodies called corpora aliena adiposa, lying free in the general peritoneal cavity. In personal communications, several men have reported finding these corpora aliena, although most men have not regarded them as particularly important. As will be shown later, these same foreign bodies, unless recognized for what they are, may be misconstrued with unnecessary surgery resulting.

A long search through contemporary textbooks reveals very little mention of epiploic appendicitis. Virchow has originally given us careful pathologic studies with particular reference to corpora aliena and Riedel of Jena wrote two papers on the subject, reporting 8 cases. Thirty years ago, Briggs, of Sacramento, California, made a thorough study of the subject and reviewed 15 cases which included 2 of his own. Both Riedel and Briggs, followed later by Bottomley, described the condition as occurring in two forms of about equal incidence, namely intra-abdominal and hernial. Bottomley insists that it usually occurs in middle or later life in persons who are more or less obese.

Varying with the locality of the affection, the symptoms may simulate those of involvement of any of the important intra-abdominal organs, such as the appendix, the gall bladder, or pelvic pathology. Vaughan states simply that "strangulated appendices epiploicae" are lesions of the alimentary tract which simulate appendicitis. Ortner states that torsion of an appendix epiploica is one of the two conditions causing gastric pain in which the diagnosis can hardly be made.

If involvement occurs in a hernial sac, it may give rise to all signs of an acute strangulation or incarceration, such as fever, vomiting, leucocytosis and pain distinctly arising in and radiating from the hernial sac. Obstructive symptoms appear early and operation is indicated at once. At operation bowel involvement may be entirely extrinsic because of the incarceration of an attached epiploic appendix.

In acute gonorrheal salpingitis, there are pain, tenderness and rigidity in the lower abdomen above the symphysis. The pain may be midline or more to one side or the other. Leucocytosis is moderate and vomiting is uncommon. Fever is usually present and usually there is a vaginal discharge which may or may not contain gonococci. Signs of inflammation around the urethra and Bartholin's gland aid the diagnosis, while pressure upon the cervix during pelvic examination produces pain and reveals tenderness in the fornices.

In ruptured ectopic pregnancy, the symptoms vary according to the age of the rupture. Here menstrual history is always of first importance, with anomalous vaginal bleeding usually present. The cervix is extremely sensitive to movement and a tender mass may be palpated in the pelvis. Before rupture, Friedman's test is of infinite value,

while after rupture, signs and symptoms become increasingly those of severe internal hemorrhage, such as rapid thready pulse, low blood pressure, pallor, and thirst. The abdomen becomes generally tender and rigid and presently becomes distended.

Ovarian cyst with a twisted pedicle, produces severe pain of a sudden onset. The patient is restless, while rigidity, tenderness, vomiting, and leucocytosis are present. Moderate shock is common. Hemorrhage from a corpus luteum of the ovary, causes severe pain but fever and vomiting are usually absent, while pelvic examination reveals very little.

Cholecystitis and cholelithiasis reveal pain and tenderness, more usually confined to the right upper quadrant. With a past history of indigestive symptoms, fever, leucocytosis and a history of jaundice aid in the diagnosis.

Most difficult differentiation is probably acute inflammation of the vermiform appendix. However, subjective symptoms are usually more marked and epigastric pain later localizing in the right lower quadrant, preceded by nausea and vomiting, is the usual course of events in ordinary appendicitis. Muscle spasm and laboratory findings may also be helpful. Although appendices epiploicae are most often found on the descending and sigmoid colon, C. F. Vale, in charge of a busy service at Receiving Hospital, Detroit, reported to me that on two occasions, he has opened the abdomen for acute appendicitis and discovered gangrenous epiploic appendicitis with a normal vermiform appendix.

CASE REPORTS

Mrs. M. H., aged 32, Case No. B30754, was admitted to the hospital on Jan. 31, 1933. Her chief complaint was pain and swelling in the left lower quadrant.

Present Illness.—Off and on for several years, this patient had had a soreness in the left lower quadrant, which had always been worse during pregnancy. Usually it was only "an aching soreness" but at times it was sharp and cramping. Three days ago this became much more severe and yesterday for the first time she noticed a swelling in this region which had increased in size until now it was quite noticeable. The pain was increased by moving around and by active movements of the baby. (The patient was seven months pregnant.) "A drawing cramping pain" was present even when the patient was quiet. Pain radiated upward toward the rib margin but there was no nausea or vomiting, no fever or chills, and no subjective urinary symptoms. The patient had had the usual number of soft stools.

Past History.—This patient had severe tonsillitis and acute articular rheumatism at thirteen years of age. During that time her heart was damaged but she had no cardiac symptoms. She had had pneumonia three times, no pleurisy, but she suffered frequently from colds and she had quinsy several years ago. She had influenza this winter. The family history was negative. The catamenia began at thirteen years of age. Her periods were the regular twenty-eight-day type until the last few years. The patient now may skip from one to three months at a time. She had always had severe dysmenorrhea with backaches for several days. The pain in the left side was not increased during menses. The patient usually flowed profusely for six or seven days.

Marital History.—The last menstrual period was July 27, 1932. Her first pregnancy resulted in spontaneous delivery of a full-term baby in April, 1926. In February, 1927, the left tube was removed because of ectopic pregnancy, at which time the right cystic ovary and appendix were excised. Normal full-term babies were delivered in March, 1928, and August, 1929.

Physical Examination.—Temperature 100° F., pulse 120, and respiration 22. The tonsils were cryptic and enlarged and chronically infected. *Chest:* The heart action was rapid; both sounds were accentuated. There were no murmurs or enlargement. *Abdomen:* The uterus was enlarged to a level three fingerbreadths above the navel. The fetus could be palpated and the fetal heart was regular and normal. There was no vaginal bleeding. There was a soft and exquisitely tender swelling extending from the level of the symphysis to well above the anterior superior iliac spine. The midpoint of the mass was almost exactly the midpoint of Poupart's ligament and the circumference of this swelling was approximately circular with a diameter of about 10 by 12 cm. Pressure anywhere on the abdomen elicited pain in this region. There was no rigidity or induration, and no tympanites except over the normal colon.

Laboratory.—Urine catheterized acid; W.B.C. 25 to 30 per high power field; a few small and large clumps; 1-plus albumin; no sugar or diacetic acid; bacteria few and few epithelial cells. Blood: W.B.C. 13,800; 84 polymorphonuclears, 16 lymphocytes. The Wassermann test was negative. Postoperatively, the urine showed 1-plus albumin; 3-plus acetone, and was loaded with epithelial and pus cells.

Operation.—Following the usual preparation, an incision was made on line with the umbilicus about 4 inches long just above the external third of Poupart's ligament. Exploration revealed a thrombosed black inflammatory mass, attached to the large bowel encased in indurated omentum. The tip of the ovary was part of the mass, but the ovary itself seemed to be normal except for some slight inflammatory reaction from the adjacent pathology. The blackened mass was separated from the thin adhesions binding it down to the mesentery, and removed by clamping, crushing, cutting, and carbolizing the stump. It was not possible to determine whether or not a lumen was present, hence the possibility of a small twisted diverticulum could not be ruled out.

Pathologic Report.—Gross: A dark oval of firm homogeneous tissue. *Microscopic:* Sections show fatty tissue surrounded by a thin layer of fibrous tissue and containing marked extravasation of blood and areas of hemorrhage. The blood vessels are dilated and filled with blood. There is an infiltration of polynuclear cells.

Diagnosis.—Acute inflammation of appendix epiploica.

Progress Notes.—The highest postoperative rise was to 100 and the day following operation, this dropped to normal and remained there throughout her hospital stay. The pulse was rather rapid but slowly returned to normal. Except for some gas and belching, the patient had a comfortable convalescence and was discharged from the hospital nine days after operation.

An interesting side light on this patient is the fact that following her normal convalescence, she delivered spontaneously in April, a normal full-term infant. Another pregnancy resulted in her sixth full-term baby in September, 1934. A year later a hysterectomy was done because of menorrhagia. A small vesicovaginal fistula showed itself on the eighth day after operation but finally healed spontaneously two months later. Hence, this patient delivered four normal full-term babies since her left tube and right ovary were removed in 1927.

The second case was the patient of another surgeon. Mrs. M. R., aged 26, Case No. B70997. Her chief complaint was indigestion and sour stomach.

Present Illness.—For the past three weeks this patient had been bothered with indigestion and sour stomach. She had had tenderness in both lower quadrants, but more on the right side. An occasional cramping pain remained in the right lower quadrant. She had had headaches for two weeks, but no nausea or vomiting. The appetite had been poor for four or five days. The last menstrual period was March 11.

Marital History.—Menstruation began at the age of nine and one-half years. The periods were usually every twenty-eight days, lasting four to seven days. M. R. had never been pregnant.

Physical Examination.—The physical examination revealed a well-developed, obese, white female. Temperature, 98° F.; pulse, 80; respiration, 18; blood pressure, 104/90. *Abdomen:* There was tenderness in both lower quadrants over the adnexa.

Laboratory.—R.B.C., 4,220,000; W.B.C., 11,200; Hb., 13.5; color index, 1; polymorphonuclears, 71; lymphocytes, 26; monocytes, 2; eosinophiles, 1. Urine, acid; specific gravity, 1,029; sugar, negative; albumin, faint trace.

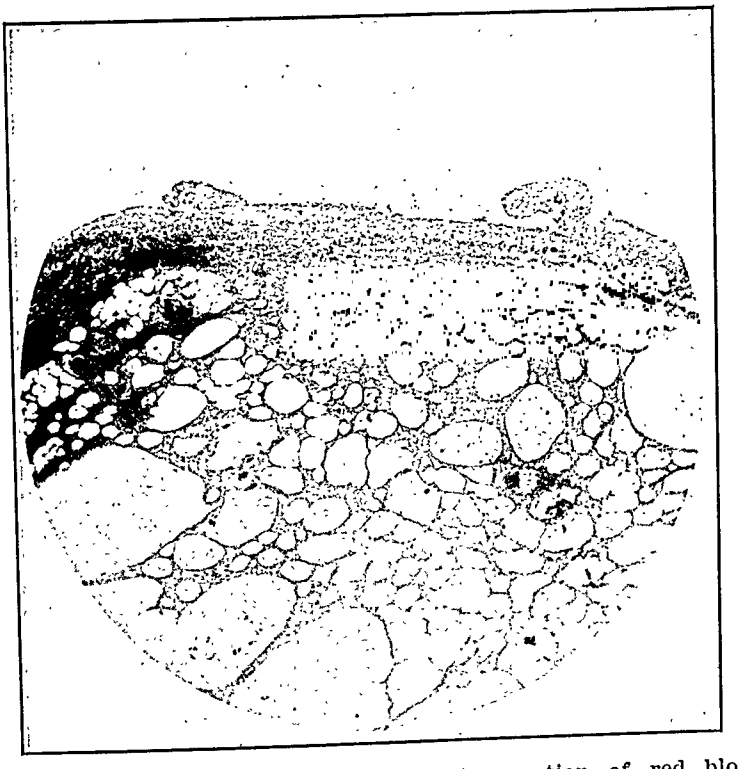


Fig. 1.—Section of peritoneal fat reveals extravasation of red blood cells and infiltration of polymorphonuclear leucocytes. There is also congestion, and the fixed tissue reveals necrotic changes.



Fig. 2.—Peritoneal fat shows fibroblastic proliferation and fibrinous exudate on the surface. Note also congested vessels and extravasated red blood cells. There is some evidence of necrosis in the surface mesothelium.

Operation.—Surgeon's note. "A midline infraumbilical incision was made. The patient was abnormally obese. The left tube and ovary were normal. The right tube showed signs of an old inflammation and lying beneath the tube embedded in fat was a brownish purple mass. It was recalled that about six months ago, the



Fig. 3.—Section of peritoneal fat shows a marked extravasation of red blood cells together with infiltration of polymorphonuclear leucocytes. The surface mesothelium is necrotic.

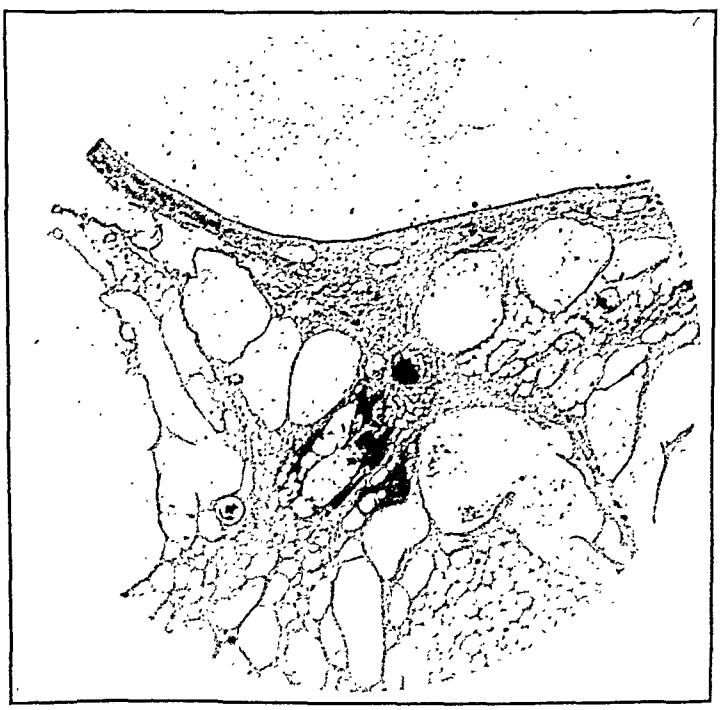


Fig. 4.—Section of peritoneal fat reveals mostly hemorrhage and congestion. On the surface there are a few fibroblasts proliferating. Fixed tissues are generally necrotic.

patient had an irregularity in menstruation, but the symptoms were not severe enough to warrant operation for ectopic. The right tube and old placental mass were removed. The appendix was then inspected and was found to be retrocecal. Definite inflammation was present. The appendix was removed following the usual technique with purse string suture.''

Pathologic Report.—Gross: Appendix measured 7.5 cm. by 0.7 cm. The tube was 7.5 cm. long and was slightly thickened. There was a moderate degree of hydrosalpinx present. Also present was a free piece of fatty tissue entirely encapsulated by hemorrhagic and necrotic material and measuring 2 cm. across. *Microscopic Diagnosis:* (1) Chronic catarrhal appendicitis, Grade II, with acute extrinsic suppurative appendicitis, Grade I; (2) moderate hydrosalpinx; (3) gangrenous and suppurating epiploic appendix.

COMMENT

In the first patient, our diagnosis was obscured by the fact that location of the difficulty was in the region of the single remaining ovary. Since the mass was palpable and because of its location, we may be excused for suspecting a twisted ovarian cyst. However, at operation it was seen that the mass would have been neither palpable nor visible if the uterus had not contained a seven months' pregnancy, which pushed the inflammatory mass snugly against the abdominal wall. Since the urine cleared up so quickly after operation, it was felt that the urinary pus preoperatively was a result of the intra-abdominal inflammation, similar to the urinary findings seen occasionally in ordinary appendicitis. Although there had been a long history of crampy soreness in the region, operation effected a cure and there has been no pain since. In the second patient, the pathology found at operation was misconstrued by the surgeon. The dark-looking, firm corpus alienum adiposum was thought to be a lithopedion, because of a peculiar irregularity of the menses six months previously, and the right tube was removed. The appendix which grossly seemed to be definitely inflamed was actually an acute extrinsic reaction resulting from gangrenous epiploic appendix.

It is probably true that only a rare case of epiploic appendicitis can be definitely diagnosed. It is usually likely that subjective symptoms are rather vague while objective signs are difficult to elicit. A middle-aged or older patient who tends to be more or less obese, with peculiar abdominal symptoms, should make us watchful. The temperature reaction is likely to be mild. The blood count is likely to be very slightly elevated with a differential normal or only suggestive. Pain and tenderness will be found more often in parts of the abdomen that seem unrelated to abdominal organs usually involved in acute inflammatory processes. This is because most appendices epiploicae, particularly of the long pedicled variety, are found on the left side of the abdomen, connected with the transverse or sigmoid colon. Although pain and tenderness, particularly the latter, may be more or less circumscribed, muscle rigidity is a late symptom.

It is certainly possible that patients who seem to recover quickly from abdominal complaints which we treat conservatively for some reason without definite diagnosis, may have suffered an inflammatory

torsion or separation of an epiploic appendix which has healed spontaneously. Undoubtedly, adhesions of the distal extremity of an epiploic appendix are due to old inflammation. These adhesive bands may give rise to symptoms of obstruction and intestinal strangulation in later life. In the event that strangulation of the appendix epiploica occurs at the neck of a hernial sac, the symptoms are usually those of incarceration.

Even though diagnosis can probably be no more than tentative because of the location of the pathology, operation is indicated. In early cases mortality should be nil, as ordinarily all that is necessary is ligation and excision of the offending appendage and closure of the abdominal wound without drainage.

CONCLUSIONS

1. Torsion and gangrenous inflammation of appendices epiploicae usually occur in middle aged or older individuals and are more frequent than a scarcity of references in medical literature would indicate.
2. In the present state of our knowledge, anything more than tentative diagnosis is impossible.
3. The end result may be spontaneous healing with formation of corpora aliena adiposa or adhesive bands and their consequences. It is important to be able to recognize these corpora aliena at operation.
4. Extrinsic involvement of contiguous organs is possible.
5. Early operation is indicated and the results should be uniformly good.

I wish to acknowledge my indebtedness to Dr. Donald C. Beaver for his assistance in the pathological studies reported above.

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THE USE OF SOLUTIONS OF ACACIA IN OBSTETRICS*

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A DECREASE in the volume of the circulating blood is a universal occurrence in shock and hemorrhage. The intravenous administration of fluids combats this deficiency in blood volume and tends to relieve the condition of shock associated with this decrease in volume of blood, whether it be associated with hemorrhage or not, provided the circulation is intact at the time of administration. Since there is no fluid that is a complete substitute for whole blood in restoring the volume of circulating blood, transfusions of blood will probably remain the ideal therapeutic procedure in the treatment of hemorrhage and shock.

The establishment of depots or "banks" of refrigerated blood is at present increasing the availability of blood transfusions. However, there are several reasons for the development and use of a safe and acceptable substitute for blood. These reasons may be summarized as follows: Considerable time will necessarily elapse before a sufficient number of dependable depots of stored blood will be available for the country as a whole. This will be particularly true in the rural areas. Unless large volumes of blood are continually in demand a constant supply of stored blood is impracticable as it deteriorates. If the blood of universal donors is not available in storage, all recipients must be grouped, which may cause the loss of valuable time in an emergency. The supply of universal donors is limited. Many cases of hemorrhage and/or shock will not require blood if an acceptable substitute is immediately available. Finally, the cost of blood is much greater than that of such a substitute as a saline solution of acacia.

The use of saline solutions of acacia has been discussed since Bayliss[1] and others instituted this therapeutic measure on a large scale during the World War. At that time Keith,[2] Bayliss,[1] and others expressed the opinion that solutions of acacia give excellent results in the treatment of shock and hemorrhage, provided properly prepared solutions are administered to patients who are not so severely shocked or exsanguinated that even blood transfusion would not control the vascular collapse. This condition exists when the blood volume is decreased to about 30 per cent.

Amberson[3] recently reviewed the whole field of blood substitutes and but brief mention need here be made of this subject.

Objections to the intravenous injection of solutions of acacia have been raised, because if given in very large volumes the gum is stored in the cells of the lobule of the liver[4] (not the Kupffer cells), thus interfering with the function of the liver. The facts that this solution increases the rate of sedimentation of the erythrocytes,[5] prevents cellular respiration by coating the erythrocytes,[6] reduces the power of the blood to combine

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, October 6 to 8, 1938.

with carbon dioxide by 5 to 10 per cent,[5] and decreases the concentration of the proteins of the plasma by possible blocking of the liver,[3] have been advanced against the employment of this solution in the treatment of patients. It has been further stated that solutions of acacia cannot maintain the colloidal osmotic pressure of the blood for more than forty-eight hours.[3] Acacia is related chemically to the antigenic polysaccharides produced by the pneumococcus and other bacteria. Maytum and Magath[7] reported one case of a patient who had a sensitivity to solutions of acacia at the time of a second injection administered five months after the first injection. This was the only evidence of an untoward reaction in a group of 3,000 patients. Except for the previously mentioned damaging effect of huge volumes of acacia on the liver as shown by Andersch and Gibson,[4] Dick, Warweg and Andersch,[8] and Hall,[9] the afore-mentioned objections are not of serious practical importance.

Stanbury, Warweg and Amberson[10] showed by experimental total plasmapheresis that solutions of acacia are relatively innocuous in the experimental animal (dog). As near as was technically possible they completely replaced the plasma by saline solutions of acacia, thus reducing the serum proteins to only 0.05 to 0.15 per cent. These dogs remained healthy and active for considerable periods of time until killed. Unfortunately no studies of the liver were recorded by these authors. Doi,[11] and Gesell, Capp and Foote (quoted by Amberson), and Schlomovitz, Rozone and Schlomovitz (quoted by Amberson) all showed that the oxygen consumption of dogs is decreased when the volume of blood is reduced by hemorrhage but that it is completely restored and maintained at normal level when the blood lost is replaced by solution of acacia.

After considering the facts mentioned in the preceding paragraph Amberson concluded, "Gum acacia is now in almost daily use in hundreds of hospitals throughout the world, and next to blood plasma unquestionably constitutes the most successful substitute for whole blood which has so far been developed."

Deaths following the injection of solutions of acacia have been reported in the literature by three writers: Olivecrona[12] (1 case reported in 1921); Lee[13] (2 cases reported in 1922), and Studdiford[14] (5 cases reported in 1937). The 3 deaths reported by the two first named writers occurred during a period when it was not sufficiently appreciated that great care must be exercised in the preparation of solutions of acacia. The more recent deaths reported by Studdiford immediately followed the use of a commercial solution of acacia different from that which he had previously employed. This author admitted that the solutions were probably toxic and stated that CoTui (who tested the solutions) "has evidence to believe the cause of the immediate reaction lies in error in preparation of the solution." The manufacturers of the solution reported in the paper by Studdiford admitted that the solution had been carmelized to color it and carmelization of solutions alone may cause toxic reactions. One of us has observed severe reactions to carmelized dextrose solutions. The solutions employed by Studdiford gave severe reactions to all of four dogs when injected intravenously.

The successful employment of solutions of acacia in the treatment of hemorrhage and shock in a number of patients that would make a large total in the aggregate has been reported by the following: Hurwitz,[15] Bayliss,[1] Keith,[2] Erlanger and Gasser,[16] Fraser and Cowell,[17] Cannon, Fraser and Hooper,[18] Rous and Wilson,[19] Drummond and Taylor,[20] Robertson and Bock,[21] Ohler,[22] Farrar,[23] Coburn and Ward,[24] Meek and Gasser,[25] Lynwood,[26] Masson,[27] Adson and McIndoe,[28] Randall,[29] Dieckmann,[30] Hartman and others,[31] Good and Boyer,[32] Good, Mugrage and Weiskittel,[33] Counseller,[34] Huffman,[5] Lowsley, Morrissey and Ricci,[35] Walker and Keith,[36] and others. These authors did not mention serious reactions or deaths as a result of the use of this solution. More than 6,000 intravenous injections of saline solution of acacia have been given to patients at the Mayo Clinic without untoward

results. Dr. H. E. Robertson[37] of the Section on Pathologic Anatomy of the Mayo Clinic stated that in no case did necropsy performed on a patient who had previously received an injection of saline solution of acacia reveal gross or histologic evidence of damage to the liver that might be attributed to this medication.

In 1929 one of us[29] reported on the use of a 6 per cent solution of acacia in normal saline in the treatment of shock occurring in obstetric practice. Since that time we have continued the use of this solution and we now wish to make a further report of its use.

During this time 4,900 obstetric patients have been observed, of whom 93 (1.9 per cent) had a sufficient degree of vascular collapse due to shock and/or hemorrhage to warrant the intravenous injection of saline solution of acacia. These patients represented 44 instances of postpartum hemorrhage, 11 of shock without hemorrhage, 11 of abruptio placentae, 11 of placenta previa, 8 of abortion with hemorrhage, 5 of hemorrhage and traumatic shock following operative delivery, 1 of ruptured uterus, 1 of purpura, and 1 of retained placenta with severe anemia. There were 5 deaths in this group of 93 patients, all occurring before 1931. Two of these patients had diabetes, which was considered to be the cause of death. One patient suffered from eclampsia and had had about 25 convulsions before admission to the hospital; 1 patient died of puerperal sepsis, and 1 had a complication of toxemia with a clinical diagnosis of carcinoma of the sigmoid. We believe it to be significant that none of the deaths occurring in the group of 4,900 patients were due to hemorrhage.

The average amount of solution of acacia administered was 533 c.c., containing 31.98 gm. of acacia. The least amount given was 300 c.c. (to 4 patients). Four patients received 1,000 c.c. or more, the greatest amount being 1,500 c.c. The greatest amount of acacia given to any one patient therefore was 90 gm. Solution of acacia has been readministered to 3 women at the time of a subsequent delivery with no untoward effect.

In 37 of the 93 patients blood was given by transfusion in addition to the solution of acacia. Twenty-nine had a single transfusion of 500 c.c., 5 had two transfusions, 2 had 3 transfusions and 1 patient 8 transfusions.

The response to intravenous injection of saline solution of acacia was satisfactory so far as the symptoms due to vascular collapse were concerned in 85 (91 per cent) and in all patients after the addition of blood.

The preparation of solutions of acacia suitable for intravenous injection is important. In the article written by one of us[29] in 1929 the details of the method of preparation of a 6 per cent solution of acacia in normal saline were given. Fortunately since that time containers of this solution may be purchased from commercial laboratories. The injection is carried out in the same manner as that which applies to the intravenous injection of fluids in general. From 25 to 40 c.c. of solution are given each minute until enough has been injected to maintain a volume of blood that will overcome the vascular collapse. If blood transfusion is to follow the injection of solution of acacia, the apparatus should first be washed out with normal salt solution.

As has previously been stated, the treatment of shock should be coordinated with methods to control hemorrhage if this condition exists. Such obstetric procedures as the following, which were employed in this group of 93 patients, may be needed to control the blood loss: Uterine massage, the administration of oxytocics, manual removal of the placenta, intrauterine packing, insertion of a colpeurynter, rupture of the bag of waters, cesarean section, hysterectomy, or Braxton Hicks' version. In those patients who have a complication of labor or delivery in which shock may be anticipated, it is frequently wise to have the treatment of this condition under way as the operative procedure is instituted.

In conclusion, it may be stated that an acceptable substitute for whole blood still serves a useful purpose in the treatment of shock and/or hemorrhage. This substitute must be quickly available, proved by large experience to be safe, and capable of restoring and maintaining blood volume. We believe that a 6 per cent saline solution of acacia is such a substitute.

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DISCUSSION

DR. H. CLOSE HESSELTINE, Chicago, Ill.—The authors admit without argument that blood is the best agent in the treatment of obstetric hemorrhage. Perhaps one might argue that greater efforts should be put forth to make blood more readily available. The University of Chicago Clinics and the Chicago Lying-in Hospital have readily available professional donors for the hospitalized patients; yet acacia and other solutions have been used in the Home Service Unit with gratifying results. In the event of serious blood loss and other serious complications these patients have been transferred to the hospital. Even though patients recover from hemor-

rhage and shock because of the use of various intravenous solutions, the amount of morbidity and the extent of the convalescent period are other factors for evaluation. Frequently enough time elapses to find a source of blood for suspected cases of placenta previa (the severe alarming ones excepted) preceding the examination for diagnosis and before the institution of therapy, and in certain cases premature separation of the placenta.

Nevertheless when blood is not immediately available for such emergencies the best possible available substitute under the circumstances is a necessity. Various solutions have been employed. Physiologic sodium chloride solution and other salt solutions are excreted rapidly. Glucose solutions, especially hypertonic ones, remain longer in the vascular tree, but have a relatively short period of action. On the other hand, sucrose solution may increase the fluid volume in the vascular system to a dangerous point. Acacia in saline solution has given good results for these authors and others have written almost as enthusiastically.

Studdiford's fatal cases received acacia in glucose solution. Dieckmann observed a fatality in a toxemic patient following the use of a saline solution free of acacia. The toxemia was not severe enough to cause the death alone. Repeated chemical analyses of blood showed complete disappearance of fibrin, and the blood did not clot. The acacia was deposited in the endothelial cells of the liver. He was surprised to find that this same material causes no trouble when administered to dogs.

It has been shown that of the acacia solutions, salt is the safest. On the other hand, to remain safe, it must be prepared very carefully and exactly. The apparatus used to administer it must be as carefully prepared as for blood transfusion. Six per cent acacia solution will not completely substitute for blood, but will aid in maintaining a blood pressure at a physiologic level. Saline acacia solution can be carried by the physician who must treat in the home without assistance and may be readily available in institutions where blood donors and blood banks are not feasible. The technique must be followed precisely, the apparatus must be prepared properly, and the indication and contraindication heeded if the best results are to be obtained.

Since saline solution of acacia is the only one recommended, is there a contraindication to its use in the presence of toxemia of pregnancy? Would hypertonic glucose solutions alone serve better and safer in combating vascular collapse in toxemic patients?

Any contribution which will enable us to lower the maternal mortality and morbidity rate is important. The subject of saline solution of acacia in the treatment of obstetric shock and hemorrhage has been revised, and a fair analysis presented. One must agree that saline acacia solution is a substitute for blood when sources of blood are not available, as demonstrated emphatically in this paper. Even though it is not an ideal substitute, when properly employed it may, by conserving life, make motherhood even less of a risk.

DR. ARTHUR B. HUNT (closing).—I am glad Dr. Hesseltine made mention of the fact that the use of acacia helps prevent morbidity in the puerperium. We feel that supplementing acacia later in the puerperium in severe anemia with blood is more effective. I am also glad he mentioned that acacia holds up the blood volume longer than saline and glucose because that is one important reason for using acacia rather than other blood substitutes. It also has the advantage of drawing tissue fluid into the circulation by its increased osmotic pressure. We have used a commercial preparation of acacia for over a year without any difficulty. Dr. J. S. Lundy, Head of the Section on Anesthesia and Intravenous Therapy at the Clinic, says that it has proved entirely satisfactory. However, now that blood is available in storage, we do not use as much acacia as formerly.

When shock is so severe that the blood pressure cannot be elicited, positive pressure may be needed to force the blood or acacia into the circulatory system, the veins being collapsed. If this is done it is unnecessary to cut down on a vein. Only once in this series of over ninety instances of hemorrhage and shock was it necessary to cut down on the vein.

DÜHRSSEN'S INCISIONS*

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THE patient who, after many hours in labor with the membranes ruptured, fails to reach complete cervical dilatation and shows evidence of exhaustion with a gradual decrease in the effectiveness of the uterine contractions presents one of the major obstetric problems. In some instances of this type, delivery may be accomplished satisfactorily following Dührssen's incisions of the cervix. This study was undertaken to evaluate the results of this procedure and to determine the dangers associated with it.

This report covers the period from Nov. 1, 1932 to Sept. 1, 1938, during which 162 Dührssen's incisions were performed. In a previous report from the Chicago Lying-in Hospital, Hunt and McGee[1] summarized 592 cases in which Dührssen's incisions were done from 1917 until November, 1932. Series have been reviewed in the literature during the past ten years by Randall,[2] Shir,[3] and Abrams.[4]

Incidence.—The 162 cases occurred during the course of 15,529 deliveries. The incidence is 1.04 per cent. In Table I, the incidence at yearly intervals is recorded. In the fifteen years previous to 1932, the incidence was 1.48 per cent as reported by Hunt and McGee. There has been a slight decrease in the frequency with which the procedure has been employed so that during the past year the incidence was 0.9 per cent. Abrams reported a 6.0 per cent incidence of Dührssen's incisions in his series; Randall, an incidence of 0.37 per cent; and Shir, 0.62 per cent.

TABLE I. INCIDENCE OF DÜHRSSEN'S INCISIONS

	TOTAL PATIENTS	DÜHRSSEN'S	INCIDENCE PER CENT
Nov. 1, 1932—June 30, 1934	4,611	53	1.2
July 1, 1934—June 30, 1935	2,909	38	1.3
July 1, 1935—June 30, 1936	2,394	22	0.9
July 1, 1936—June 30, 1937	2,341	19	0.8
July 1, 1937—Aug. 31, 1938	3,274	30	0.9
Total	15,529	162	1.0

TECHNIQUE

Adequate exposure is essential, as it is preferable to make the cervical incisions under direct vision rather than by palpation. A deep mediolateral episiotomy is performed and the cervix exposed with broad retractors. Three incisions are usually made at points corresponding to 10, 2, and 6 on the clock. If the cervix is approaching complete dilatation, bilateral incisions may be sufficient but there is greater danger of subsequent extension. The use of one incision is

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

associated with great risk of damage to the cervix. In our series, laceration or extension of the incision occurred in 7.7 per cent of the instances where three incisions were made and in 41.7 per cent where only one incision was used.

The posterior incision is made first so that its site will not be obscured by blood from the anterior incisions. The cervix is grasped posteriorly with two clamps and exposed with gentle traction. Too much traction must be guarded against or the cervix, particularly if edematous, will tear. The incision is made between the clamps and should extend to the fornix. Adequate incision protects the remainder of the cervix and the lower uterine segment from laceration. The incisions corresponding to points 10 and 2 on the clock are made in a similar manner.

After delivery of the infant and placenta, the cervix is exposed and the edges of the cervix grasped for inspection and repair. The edges of the cervical incisions are approximated beginning at the upper angle of the incision with loosely tied, interrupted sutures of No. 2 chromic catgut. From two to four sutures are usually required. In the presence of infection or severe shock, the incisions may be left unrepaired and will usually heal surprisingly well.

Care should be taken to prevent blood loss. Unless guarded against, there may be considerable bleeding from the episiotomy wound during the course of a prolonged operative procedure though there is often little if any bleeding from the cervical incisions themselves.

INDICATIONS

In general, Dührssen's incisions are indicated where delivery becomes necessary in the interests of the mother in the presence of a completely effaced but incompletely dilated cervix. In many instances a multiplicity of factors are responsible for the decision to incise the cervix. These usually include (1) failure of progress after a prolonged period of labor, (2) approaching exhaustion with irregular and ineffective uterine contractions, and (3) evidence of fetal distress. In analyzing the cases in this series, an attempt was made to pick out the predominant indication for the procedure in each case. These are listed in Table II. In all instances where there was an indication from the standpoint of the fetus, there was also a maternal indication present.

Cervical dystocia was given as the indication in approximately one-third of the group. In all probability this does not represent in every case an undilatable cervix, but in all of these patients the cervix was more than usually rigid and firm. Poor adaptation of the fetal head to the cervix and ineffective uterine contraction were undoubted factors in some instances in the failure of the cervix to dilate. These patients represent a group, however, in which there was no other reason, per se, to forecast difficulty at the onset of or early in labor and in whom failure of the cervix to dilate was the outstanding abnormality.

TABLE II. INDICATIONS

MATERNAL		FETAL	
Cervical dystocia	55	Irregular fetal heart	12
Soft tissue dystocia	14	Failing fetal heart	8
Edema of cervix	7	Presence of meconium	2
Failure of progress	48	Large baby	1
Exhaustion	15	Funic souffle	1
Uterine inertia	13		
Combined maternal and fetal	24		

SECONDARY FACTORS	
Toxemia (1 eclampsia)	13
Cephalopelvic disproportion	13
Cardiac disease	1

Soft tissue dystocia is used in Table II to denote the situation in which the progress of labor seems to be delayed by the presence within the bony pelvis of resistant, thick pelvic tissues. Many of these patients were of the stocky, heavy

type described as representative of the dystocia dystrophy syndrome. Dystocia of this type was present in 14 of the patients. Eight more of the patients (Table III) were classified in the dystocia dystrophy syndrome type but other factors were more definitely described as indicating the cervical incisions in their management.

TABLE III

Pelvis:		
Contracted	31	19.1%
Dystocia dystrophy syndrome type	22	13.6%
Fetus:		
Average weight	3410 gm.	
Under 2,500 gm.	9	
Over 4,000 gm.	17	
Pains:		
Weak or irregular	69	42.6%
Adequate	93	57.4%

TABLE IV. AGE DISTRIBUTION

YEARS	NUMBER	PER CENT
17-19	9	5.5
20-24	38	23.4
25-29	62	38.2
30-34	37	22.8
35-39	14	8.6 (32.6)
40-42	2	1.2

PARITY

PARA 0	PARA I	PARA II	PARA III
144—88.9%	14—8.7%	3—1.8%	1—0.6%

Edema of the cervix sufficient to obstruct the progress of the labor was present in 7 instances. In 20 instances (Table VI) cervical edema was a contributing factor. Undoubtedly edema of the cervix is due in most instances to the slow progress of labor in these patients resulting in interference with the local circulation so that it should not be considered as the primary complication. The presence of edema does decrease the probability of complete dilatation being reached and it usually becomes a progressive condition ending in necrosis of the cervix. It is for this reason then that Dührssen's incisions become indicated in these patients where edema of the cervix complicates a prolonged labor.

Failure of progress with incomplete cervical dilatation was the indication for incision of the cervix in 48 patients. In many of these patients, the fetus was in a posterior position, and due to the partial deflection of the fetal head with poor accommodation between the fetus and the birth canal, rotation was slow and incomplete. After a prolonged period of labor often complicated by inadequate uterine contractions, progress ceased for a period of several hours. When such a situation develops in spite of adequate supportive treatment and rest, it is frequently safer for both the mother and infant to complete the delivery artificially. In some instances in this group, the development of evidence of fetal distress was the deciding factor as it was felt that without interference the risk for the infant would be increased.

Maternal exhaustion was the predominant factor in 15 instances. It is probable that these patients might be grouped with those showing a failure of progress but the presence of exhaustion was more marked in this group and they are accordingly listed separately. It is to be understood that exhaustion developed in spite of adequate sedation and supportive therapy and was the result of the prolonged period of labor in patients who may have been below par physically.

Uterine inertia was the indication in 13 patients although the uterine contractions were classified as weak or irregular in 69 (42.6 per cent) of the group (Table III). It is suggested that induction of labor may have been a factor in some of these cases.

Complicating conditions, such as the toxemias of pregnancy and heart disease, may be secondary factors in the decision to perform Dührssen's incisions. In 13 patients in this series toxemia of pregnancy was present and was an undoubted factor in hastening the decision to incise the cervix; but in no instance was the procedure undertaken because of the toxemia alone. Similarly in one patient with cardiac disease, Dührssen's incisions were done at an earlier time than would have been indicated had it not been hoped to spare the patient the strain of an unduly prolonged labor.

The incidence of contracted pelvis is higher than usual in this series. Thirty-one patients (19.1 per cent) of the group (Table III) showed some degree of pelvic contraction. In 13 of these patients, cephalopelvic disproportion of mild degree may well have been a factor in the prolonged labor.

The infants were in many instances larger than usual (Table III). Although the average weight was 3,410 gm. which is not much above average figures; 17 weighed over 4,000 gm., 61 weighed over 3,500 gm., and 9 weighed under 2,500 gm.

CONDITIONS

Of equal importance with the indications for which this procedure may be performed are the conditions under which it is justified. Dührssen's incisions should be looked upon as a major obstetric procedure to be done only in a suitable environment by a trained obstetrician. The cervix must be completely effaced although dilatation is incomplete. An adequate period of labor without further cervical dilatation should have elapsed unless sudden exigencies demand the completion of the delivery. The situation should be such that delivery is indicated and possible except for the condition of the cervix.

AGE AND PARITY

The age of the patients in this series varied from 17 to 42 (Table IV). The largest group was between 25 and 29 years. Approximately one-third were 30 years or older. This is significant when one considers that only 18 of the group were multiparas; 88.9 per cent of the patients were primiparas. In one-third of the multiparas the condition of the fetus was the determining factor in the decision to perform Dührssen's incisions while there was an indication from the standpoint of the fetus in only 14 of the 144 primiparas.

ONSET AND DURATION OF LABOR

The incidence of induction of labor was approximately twice that recorded for all the patients delivered during the same period of time (Table V). Approximately one out of every 5 patients upon whom Dührssen's incisions were done had either a medical or mechanical induction of labor. Labor was induced medically in 14.8 per cent of the group and mechanically in 4.3 per cent.

TABLE V A. ONSET OF LABOR

	NO.	INDUCED	MEDICAL	MECHANICAL
Total series	15,529	1,572—10.1%	1,241— 7.9%	331—2.1%
Dührssen's	162	31—19.3%	24—14.8%	7—4.3%

TABLE V B. DURATION OF LABOR, AVERAGE 37.8 HR.

	TOTAL NO.	UNDER 25 HR.	25-50 HR.	OVER 50 HR.
Primiparas	144	18—12.5%	101—70.1%	25—17.4%
Multiparas	18	11—61.1%	7—38.9%	
			OVER 25 HR.	
Dührssen's	162		133—82.7%	
Total series	15,529		983— 6.3%	

The average duration of labor was 37.8 hours (Table V). Labor was prolonged beyond twenty-five hours in 82.7 per cent of the group while 11 of the 29 patients with a labor less than twenty-five hours in length were multiparas. The incidence of prolonged labor (twenty-five hours or over) in the total series of deliveries during the same time interval was 6.3 per cent. The longest labor in the group was ninety-nine hours with labor lasting over fifty hours in 25 (17.4 per cent) patients.

RUPTURE OF MEMBRANES

The membranes were ruptured artificially in 60 of the 162 cases. In most instances this was done after the cervix had become partially dilated and the progress of labor had ceased. The membranes were ruptured for an average of 23.5 hours before the cervical incisions were performed.

CONDITION OF CERVIX

The degree of cervical dilatation varied from 3 to 9 cm. (Table VI). In 70.4 per cent of the cases the cervix was dilated 7 to 8 cm. Edema of the cervix, usually the anterior lip, was present in 17.3 per cent.

TABLE VI

Rupture of Membranes			
	NO.	PER CENT	DURATION
Artificial	60	37.0	23.5 hr.
Natural	102	63.0	
Condition of Cervix			
DILATATION			EDEMA
3-4 cm.	4— 2.4%		
5-6 cm.	37—22.8%		27—17.3%
7-8 cm.	114—70.4%		
9 cm.	7— 4.4%		

POSITION OF FETUS

The fetal positions encountered show a wide variation from the distribution usually given in the textbooks. In only 14 (8.7 per cent) instances was the occiput anterior to the transverse (Table VII). Posterior positions of the occiput

TABLE VII. POSITION OF FETUS

	NO.	PER CENT	
Occiput anterior	14	8.7	
Occiput transverse	60	37.0	87.6%
Occiput posterior	82	50.6	
Breech presentation	5	3.1	
Brow presentation	1	0.6	

were found in one-half of the cases and together with the occiput transverse positions comprise 87.6 per cent of the group. Undoubtedly the presence of an occipitoposterior position with failure of normal rotation was a major factor in the prolonged labor and arrested progress shown by this group of patients. Breech presentations were encountered in 3.1 per cent of the patients, an essentially normal incidence. There was one brow presentation.

METHOD OF DELIVERY

The incision of the cervix was followed by immediate delivery in all instances. It has been our policy that any situation which justifies the performance of Dührssen's incisions should also necessitate immediate delivery of the

infant. This was accomplished by forceps extraction in 157 of the 166 deliveries (Table VIII). Version and extraction was employed in 6 instances and on 3 occasions the delivery was accomplished by breech extraction. There were four instances of twins. The incidence of low forceps was 12.0 per cent. Delivery followed midforceps application in 65.1 per cent of the group. High forceps application, where the fetal head was above the ischial spines but not floating, was performed in 17.5 per cent.

TABLE VIII. METHOD OF DELIVERY

	NO.	PER CENT
Low forceps	20	12.0
Midforceps	108	65.1
High forceps	29	17.5
Version and extraction	6	3.6
Breech extraction	3	1.8
Total	166	
Twins	4	
No. of patients	162	

BLOOD LOSS

The amount of estimated blood loss varied from 100 to 1,200 c.c. (Table IX). The average for the group was 365 c.c. A blood loss of 500 c.c. or more was recorded in 26 of the deliveries (16.0 per cent). This is approximately the same incidence (14 per cent) as that recorded by Hunt and McGee in the last 100 patients of their series and while high represents an improvement over the general average of their total series (28.2 per cent). Constant attention directed toward control of hemorrhage from the episiotomy wound and from the cervical incisions, and the frequent use of intravenous pituitrin or ergonovine to control hemorrhage from the atonic uterus frequently encountered in this group of patients, are probably important factors in decreasing the amount of hemorrhage.

An attempt was made to determine what factors might be responsible for the post-partum hemorrhages which did occur. As shown in Table IX the number of cervical incisions might at first sight be considered important as there was an

TABLE IX. ESTIMATED BLOOD LOSS

Least, 100 c.c. Average, 365 c.c. Greatest, 1,200 c.c.

FACTORS	NO.	POST-PARTUM HEMORRHAGE	
		NO.	PER CENT
No. of incisions			
1	12	0	0.0
2	72	8	11.1
3	78	18	23.1
Dilatation of cervix			
3-6 cm.	41	5	12.1
7-9 cm.	121	21	17.3
Edema of cervix			
None	135	21	15.5
Present	27	5	18.5
Character of pains			
Weak or irregular	69	7	10.1
Adequate	93	19	20.3
Method of delivery			
Low forceps	20	4	20.0
Midforceps	108	14	12.9
High forceps	29	8	27.6

increased incidence of hemorrhage when 3 incisions were made. It must be remembered, however, that extension of the incisions occurred more frequently in the instances where one or two incisions were made and that such extensions increase the danger of hemorrhage. Three incisions were always made where the cervix was dilated less than 6 cm. yet the incidence of post-partum hemorrhage is greater in the group with a cervical dilatation of 7 to 9 cm. Edema of the cervix did not appear to be a factor in the production of hemorrhage, contrary to the conclusions drawn by Hunt and McGee. The patients with weak or irregular uterine contractions might be expected to have a poorer uterine tone and consequently an increased blood loss. The incidence of post-partum hemorrhage in the group with adequate uterine contractions, however, was twice that in the group where the contractions were weak or irregular. The difficulty of the delivery subsequent to the Dührssen's incisions may be a factor in determining the amount of blood loss. Post-partum hemorrhage occurred subsequent to high forceps delivery in 27.6 per cent whereas in mid-forceps and low forceps delivery the incidence was 12.9 per cent and 20.0 per cent, respectively.

The placenta was removed manually in 30 instances (18.5 per cent), usually because of hemorrhage and at times incidental to exploration of the uterine cavity. No cases of uterine rupture were recorded. Simple expression of the placenta was accomplished in 125 instances (77.2 per cent) and the placenta was delivered by the Crédé maneuver in 7 instances (4.3 per cent).

MORBIDITY AND MORTALITY

As would be expected in a group of cases such as these, the morbidity is high (Table X). Over one-fourth of the patients (27.2 per cent) showed a febrile morbidity according to the British Standard. This may be compared with a rate of 7.5 per cent according to the same standard for 5,615 consecutive patients delivered in the hospital.

There were no maternal deaths in this series. There have been 297 consecutive instances of Dührssen's incisions up to September 1, 1938, without a maternal death. There has been only one death in the last 390 cases.

TABLE X

	NO. OF PATIENTS	MORBID	PER CENT
Maternal Morbidity			
Dührssen's series	162	44	27.2
Chicago Lying-in Hospital 7/1/36—8/30/38	5,615	421	7.5
Maternal mortality—0			
Fetal Mortality			
	NO. OF INFANTS	DEATHS	PER CENT
Dührssen's series	162	21	13.0
Chicago Lying-in Hospital 5/25/31—1/137	17,728	773	4.4

FETAL MORTALITY

There were 21 fetal or neonatal deaths (Table X) in the series. This results in a mortality rate of 13.0 per cent. The mortality rate for 17,728 consecutive deliveries in the hospital is 4.4 per cent so that the rate is increased approximately three times in this group. It is to be noted that in 8 of the 21 deaths fetal distress was the essential indication for the Dührssen's incisions. It is impossible to estimate the number of babies which may have been saved by intervention before conditions became precarious.

There were no monstrosities in the group. Two of the deaths occurred in premature infants. None were pre-viable. The method of delivery was by low forceps in 3 instances; midforceps, 11; high forceps, 5; version and extraction and breech extraction, 1 each.

FOLLOW-UP STUDIES

Information was available concerning the post-partum condition of the cervix in 100 of the 162 cases (Table XI). The cervix was well healed in 41.4 per cent of the total group. It was poorly healed in 7.4 per cent and deep scars were present in 12.9 per cent.

Three of the patients returned to the clinic because they were unable to become pregnant again. No record of subsequent abortions was obtained. There have been 19 pregnancies concerning which we have knowledge in this group of patients. There have been 16 deliveries in the hospital among these patients (Table XI). The average interval between the performance of the Dührssen's incisions and the second delivery was 23.9 months. The average duration of

TABLE XI. FOLLOW-UP STUDIES

	NO.		PER CENT
CONDITION OF CERVIX:			
Well healed	67		41.4
Poorly healed	12		7.4
Deep scars	21		12.9
No record	62		38.3
SUBSEQUENT HISTORY:			
Sterile 3	Abortions 0		Pregnancies 19
	NO.	COMPLICATIONS	FETAL DEATHS
SUBSEQUENT DELIVERIES:			
Natural	9		
Low forceps	2		
Midforceps	3	Prolapsed cord	1
Breech extraction	1	Prolapsed cord	
Dührssen's	1		
	16		1
Average duration of labor, 10 hours			
Average interval between labors, 23.9 months			

labor was ten hours. One patient delivered twice, the first delivery being complicated by prolapse of the cord and resulting in a stillbirth. This was the only fetal mortality in the group. Nine patients delivered naturally, there were 1 breech extraction and 5 forceps deliveries. In one instance a second Dührssen's incision was performed. These 2 deliveries were twenty-six months apart. The first labor lasted 49.5 hours with adequate uterine contractions and a breech presentation. The infant was stillborn following breech extraction subsequent to 3 incisions in a cervix 8 cm. dilated. The second labor was complicated by an occipito-posterior position with poor uterine contractions. It was terminated when the cervix was 7 cm. dilated after 25.5 hours of labor by 3 Dührssen's incisions and midforceps extraction because of the development of irregular fetal heart tones. The patient and her infant left the hospital in good condition.

SUMMARY AND CONCLUSIONS

This review of 162 instances in which Dührssen's incisions of the cervix preceded delivery shows that the procedure is not without danger. It should be considered as a major obstetric operation indicated only in carefully considered circumstances where termination of labor becomes imperative in the interests of either mother or infant. It should not be postponed, however, until the condition of the patient and her baby increases the danger associated with its performance. Dührssen's

incisions are not to be considered at the onset of labor as a method of facilitating the delivery. The following statements concerning their employment seem justified:

1. Dührssen's incisions are indicated in a limited group in instances where the cervix is effaced but incompletely dilated.

2. In most instances indications for their use arise in the presence of prolonged labor with failure of cervical dilatation and the development of maternal exhaustion and uterine inertia.

3. The unrotated or incompletely rotated occipitoposterior position is a factor in the production of conditions indicating Dührssen's incisions.

4. Dührssen's incisions are indicated twice as frequently following induction of labor as they are subsequent to the natural onset of labor. Induction of labor in the presence of a firm, long, undilated cervix is often dangerous from this standpoint.

5. The danger of hemorrhage subsequent to incision of the cervix is increased where difficult operative delivery is necessary. It is always a real danger as shown by a 16 per cent incidence of hemorrhage over 500 c.c.

6. Three cervical incisions are associated with less danger of extension or cervical laceration than where one or two incisions are made.

7. The morbidity of 27.2 per cent associated with patients in this group is high. Infection should not be ignored even though there were no maternal deaths in this series.

8. The fetal mortality of 13.0 per cent is high but the review suggests that some fetal lives have been saved.

9. Subsequent obstetric difficulty is not demonstrably increased by the performance of Dührssen's incisions.

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DISCUSSION

DR. LAWRENCE M. RANDALL, Rochester, Minnesota.—Some years ago I wrote a paper on this subject entitled, "Hysterostomatomy," which according to the medical dictionary is the correct term for Dührssen's incisions. The latter term has, however, been associated with this obstetric procedure for so long a time that its use should probably be continued. Our incidence for the use of this procedure is in the neighborhood of 1 per cent.

There are one or two points in regard to this procedure that I think should be emphasized. In the first place I am sure we should give these patients a sufficient test of labor to prove definitely that the cervix is not going to dilate. It must also be emphasized that unless complete effacement of the cervix exists that Dührssen's incisions should not be done. The reason for this is obvious, for if the cervix is not completely effaced the danger of hemorrhage and extensive lacerations is greatly increased. The presenting part should be definitely engaged and there should not be any great disproportion in size between the presenting part and the pelvis. Dr. Huber has said that he prefers to do three incisions in all cases. We have varied from this procedure. Not infrequently it will be found that the posterior portion of the cervix is very long. In these cases an incision of this long posterior lip from the os to the fornix may sufficiently enlarge the os to permit of

delivery of the presenting part through the cervix. After making this posterior incision, if it becomes apparent that the cervix is not sufficiently dilated, then the anterior incisions may be made. It seems logical after this procedure has been performed to proceed immediately with delivery rather than to wait for the natural expulsive efforts.

DR. LOUIS RUDOLPH, CHICAGO, ILL.—Cervical dystocia is a misnomer, and has no place in obstetrics. It is used in such a manner that the cervix would appear to be separated anatomically and physiologically from the rest of the uterus. The cervical changes are actually indices of the changes of the uterus as a whole, or, in other words the cervical changes tell us what is taking place in the lower uterine segment and the corpus.

Now, cervical dystocia, as the term is used, means either functional or mechanical dystocia (cervical stenosis). The mechanical dystocia is a rare complication during labor. In prolonged labor, we are, however, frequently confronted with a functional dystocia in which we have a pathologic physiology of the uterus as a whole. When a functional cervical dystocia complicates a labor, we can state that spontaneous rupture of the uterus will not occur, unless pressure necrosis takes place.

Dührssen's incisions and operative delivery are serious operative procedures, and fraught with serious potential possibilities which is agreed to by Dr. Huber. He reports a fetal mortality of 13 per cent and no maternal mortality.

At the Cook County Hospital, we are conducting an investigation of prolonged labor with the requirement of complete cervical dilatation before undertaking operative delivery. Our fetal mortality is 8 per cent and there has been no maternal mortality.

The question arises, is it worth while to jeopardize the parturient by Dührssen's incisions plus operative delivery? It can be readily appreciated that the untrained accoucheur may increase the fetal and maternal mortality by this method of delivery. If it gives a fetal mortality of 13 per cent in the hands of the expert accoucheur, is it justifiable to jeopardize the parturient?

I believe that awaiting the second stage of labor before instituting operative delivery is still the safest procedure for the trained obstetrician, as it is for the general practitioner. If Dr. Huber had awaited the second stage of labor and then performed operative delivery, I believe his fetal mortality would not have been any higher, and the risk to the parturients less.

A very common complication of prolonged labor is constriction ring dystocia, which should be recognized before making the cervical incisions by a proper intrauterine examination. In the presence of a constriction ring then the Dührssen technique is contraindicated. In many cases following Dührssen's technique, we find that we have a difficult forceps delivery and frequently find the parturient going into shock during or after the delivery of the child. When a difficult forceps operation in an apparently normal cephalopelvic relation is followed by shock, we can assume that a constriction ring was present.

DR. J. L. BUBIS, CLEVELAND, O.—If the cervix has been taken up, but there is a tight external os dilated only to 2 or 3 cm. in diameter, you may be able to wait for twenty-four or even forty-eight hours, but if then the cervix will not dilate any more, it may be important to terminate labor. If we can apply forceps first and then do the Dührssen's incision, it makes the procedure less hazardous and difficult. The forceps are in place and you can go ahead with delivery. It is not very often that you can pull the cervix down as Dr. Huber has shown and make the Dührssen's incisions according to that technique.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I disagree with Dr. Rudolph. Of the two types of cases that might need some sort of manual dilatation or cutting of the cervix, the first would be the real Bandl's ring. In these cases, I would certainly advocate cesarean section if it is possible, but in some cases an incision is necessary. The second indication is in placenta previa or abruptio placentae.

Of course, if the head of the baby is a perfect hemisphere presentation, dilatation of the cervix and effacement should be exactly symmetrical. If there is an ovoid presentation, effacement is difficult, and one side is thinner than the other long

before the start of labor. The result is that you get tears of the cervix, not anteroposteriorly, but laterally. This is because an ovoid presentation always dilates the cervix more on one side than the other, and the weakest spot is the one to tear.

I do not like three incisions. It seems to me it is wiser to cut the very thin spots—a little bit of the thin spot on each side. You will get a much better cervix afterwards. You may have to cut a little farther up, but you will have two cuts instead of three.

DR. HUBER (closing).—We have not felt that Dührssen's incisions should in any way compete with cesarean section, and that Dührssen's incisions should be reserved for those patients who during the course of labor have unanticipated difficulty. We have felt that we have been conservative in choosing Dührssen's incisions for the patients in this group. We believe that by doing Dührssen's incisions some infants have been saved that would otherwise have been lost. We must anticipate a considerably higher fetal mortality in such a group than we would have in all cases on the service.

We have very little trouble in obtaining adequate exposure of the cervix, and these incisions can usually be performed under direct visualization. I believe that less difficulty will be encountered if the incisions are made before the forceps are applied, as the presence of the forceps inside the cervix does interfere with adequate exposure.

MYOMECTOMY DURING PREGNANCY*

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FIBROIDS of the uterus are not common during pregnancy. The incidence has been variously estimated from 0.5[1] to 0.19 per cent.[2] The reason for this relative infrequency lies in the fact that pregnancy is more common under thirty-five years of age, while fibroids do not usually attain clinical significance until after this age. It is only when pregnancy occurs in relatively older women or when fibroids develop unusually early, that the presence of such fibroids may complicate the pregnancy.

It is a well known clinical fact that fibroids increase in size during the course of pregnancy. Such enlargement has been variously attributed to (1) hypertrophy and edema of the tumor, (2) hyperplasia with edema, (3) actual growth concomitant with uterine growth. Emge[3] believes that the enlargement is a true growth phenomenon and believes it to be a temporary response due partly to a functional hypertrophy of the muscle fiber and partly to the increased vascularity. This would account for the well known regression which takes place in association with normal uterine involution.

The overwhelming majority of fibroids complicating pregnancy have no clinical significance. Mostly they do not achieve a size sufficient to interfere with the normal progress of labor nor are they located in the cervix or lower uterine segment where encroachment upon the birth

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

canal would render delivery difficult or impossible. Degeneration of such fibroids is also uncommon due probably to the increased vascularity and the growth stimulus which accompanies pregnancy. Likewise it is only the occasional subserous or pedunculated tumor which undergoes degeneration or hemorrhage from necrosis. Acute infection is also uncommon.

A small percentage of fibroids require removal during pregnancy because of acute degeneration, pain, infection, twisted pedicle, or a combination of at least moderate size and mechanical encroachment upon the birth canal. This percentage has been variously estimated.

Campbell,[4] in an analysis of the Johns Hopkins material, found only four myomectomies in a series of 82 pregnancies complicated by fibroids. Watson[2] reported only 3 myomectomies in 157 and, since 2 of these aborted, concludes that myomectomy is "likely to cause abortion." He therefore believes that myomectomy should be avoided at least until viability, at which time he prefers myomectomy and cesarean section.

While palliative treatment may be recommended for those fibroids which block the birth canal, those which undergo moderate degeneration, and those which apparently cause only pain, such a recommendation would seem to be ill-advised for twisted pedicle, acute degeneration, or active infection.

Mussey and Hardwick[1] found it necessary to operate upon 32 out of 297 instances of fibroids in pregnancy at the Mayo Clinic. Twenty-one of this series of 32 showed evidence of acute degeneration, 7 were removed because of impaction in the pelvis, 3 because of previous miscarriage, and 1 because of threatened miscarriage. Twelve of these 32 patients miscarried, 3 had premature labor, and 17 delivered at term.

It has become well recognized that pregnancy is no contraindication to laparotomy for any intraabdominal pathology which requires immediate surgical intervention. It has been previously shown by one of us[5] that appendectomy during pregnancy is comparatively safe for both mother and fetus. Lackner and Tulsky[6] report 76 laparotomies for various types of intraabdominal pathology. Only four abortions (5.3 per cent) occurred in this group. It is a significant fact that all of these occurred in patients who required operation during the first trimester of pregnancy.

Eighteen pregnant women were subjected to myomectomy for various indications during the past fifteen years at the Michael Reese Hospital. During this time there were 21,686 deliveries; a frequency of 1:1,205 deliveries. It should be noted that 11 of these myomectomies were performed in the last four years, during which time there were 6,266 deliveries, an incidence of 1:570. This frequency, which is more than double that of the entire group, may be attributed to the fact that the indications for myomectomy during pregnancy are becoming more clearly defined, and also to the fact that surgery is resorted to more readily since it has become evident that such surgical interference is comparatively safe for both mother and fetus.

Age.—The age of the patients ranged from 23 to 39, the average age being 31 years. This is four years older than the average age of women delivering at the Michael Reese Hospital and bears out the fact that fibroids are more frequently found in the older age group.

Parity.—Twelve of the patients in this group had had no previous pregnancy. Three had each had 1 previous miscarriage, 2 had each had 1 full-term pregnancy, and 1 gave a history of 1 full-term pregnancy and 2 miscarriages. These figures would seem to indicate a low fertility rate. It has been frequently stated that the presence of fibroids causes sterility and frequent miscarriage. The theory has also been advanced that sterility leads to the development of such fibroid tumors. A careful analysis of the patients in this series fails to throw any light upon this subject. So many other factors, such as late marriage, economic status, the practice of contraception, etc., enter into the evaluation of such deductions, that it would seem unwise to draw any conclusion on this phase of the subject.

Duration of Pregnancy.—The duration of pregnancy ranged from eight to thirty-two weeks. Eight patients were in the first trimester of pregnancy. Eight were in the second trimester, and 2 were in the third trimester.

Symptoms.—Fifteen patients in this series complained of severe pain, 2 complained of rectal pressure, 4 of severe dysuria, and 9 complained of abdominal tenderness.

Indications for Surgery.—Six patients were operated upon because of pain, tenderness, fever and leucocytosis; 1 because of pain, tenderness and fever without leucocytosis; and 1 because of pain, tenderness and leucocytosis without fever. Four were operated upon because of pain; only 3 were operated upon for twisted pedunculated tumors; 2 for large cervical fibroids; and 1 for a low-lying fibroid which had become incarcerated in the hollow of the sacrum.

Pathology.—In 7 patients the fibroids were intramural and in 9 patients they were subserous. Four of these latter were pedunculated, the pedicle having been twisted by torsion in each instance. Three which were subserous were located low in the uterus at the level of the lower uterine segment. In addition there was 1 large cervical fibroid, 2 large intraligamentary fibroids, and 1 cornual fibroid. Multiple myomectomies were performed six times.

Microscopic examination of the 23 fibroids removed in this series of 18 patients showed definite and marked pathologic changes in 18; 10 of these had undergone acute degeneration, 4 showed acute hemorrhage in addition to the degeneration, 2 showed marked necrosis, and 2 had undergone acute infection with pus formation. Acute pathologic changes warranting myomectomy had developed in each instance in this group.

There remain 5 patients in whom microscopic examination of the fibroids removed showed no such pathology. An analysis of these fibroids reveals that one was a twisted pedunculated tumor in which the myomectomy was performed promptly after the twist occurred and before any degenerative changes had taken place. A second was removed because of pain. This was a moderately large subserous fibroid which, in view of the lack of degenerative changes and the lack of other symptoms and physical findings, might well have been left undisturbed. The last 3 in this group were removed because of location and rate of growth. One of these was an intraligamentary tumor, and the other 2 were large, low-lying posterior wall fibroids which filled the cul-de-sac. One of these was incarcerated.

It has been stated by Lynch[7] and others that the large low-lying posterior wall fibroid is the type most likely to cause dystocia during labor. Furthermore these authors feel that since these are most difficult to remove without producing excessive trauma to both uterus and fetus, they are best let alone until term; at this time it is recommended that cesarean section plus myomectomy or hysterectomy be performed. In none of these in this series was any such technical difficulty encountered, nor was the pregnancy interfered with or disturbed.

Postoperative Course.—Fourteen of the patients were given ¼ gr. of morphine sulphate hypodermically every four to six hours for three to seven days postoperatively. We believe that this routine keeps the uterus at rest and prevents the occurrence of uterine contractions of a degree sufficient to produce miscarriage and premature labor. Two of the patients who were not given this routine complained of severe and painful uterine contractions, which subsided promptly with the administration of morphine sulphate. One patient, a nullipara of 32 years of age in the fourteenth week of her pregnancy, aborted on the fourth postoperative day in spite of continuous morphine medication. This followed the removal of a

cornual fibroid. The uterus was emptied digitally and recovery was uneventful. There was one other miscarriage in this series. This patient, described above as the one in whom myomectomy might have been properly deferred, developed a mild peritonitis with secondary ileus, bled moderately for one week following which the uterus was emptied. Post-partum hemorrhage did not occur in any instance. In only one of the other patients myomectomy followed by morbidity is reported, a mild case of pyelitis with fever of one day's duration. There were no maternal deaths. The average stay in the hospital was twelve days.

Course of Pregnancy.—Sixteen patients carried the pregnancy to term. Four delivered spontaneously, 4 were delivered by outlet forceps, 2 by low forceps, 2 by manual rotation and low forceps, and 1 by midforceps. Cesarean section was performed twice, 1 being done for a placenta previa centralis and the second an elective cesarean section in a 37-year-old primipara with a justo minor pelvis. The last patient was delivered by version and extraction because of a uterine tetany which was produced by 3 minims of pituitrin. This was a 33-year-old para ii who developed a uterine inertia during the second stage of labor. Promptly after the administration of the pituitrin, the uterus became tetanically contracted and the heart tones became faint and irregular in spite of complete surgical anesthesia with ether. A living full-term fetus was extracted following version, and the subsequent course of mother and baby was uneventful.

Fourteen of the 16 babies were normal. There was one stillbirth. This was in a 37-year-old nullipara who was allowed to go thirty-five days past her calculated due date. Heart tones disappeared during the first stage of labor and the baby was stillborn, being delivered by midforceps. One baby showed congenital abnormality, absence of the tarsal bones of the left foot and the phalanges of the left hand.

DISCUSSION

This is an analysis of 18 myomectomies performed during pregnancy without maternal mortality and with only 2 miscarriages. In all but 1, these fibroids were "clinically significant," and showed in addition the symptoms of acute degeneration or necrobiosis, sudden twist of the pedicle, or threatened dystocia because of size and location. We cannot agree with Watson that even under such conditions myomectomy should be deferred and the pregnancy carried to viability. While this series is small, there is no evidence of injury to the fetus when the pregnancy continues undisturbed, nor is there any apparent hazard of premature labor. Simple myomectomy followed by subsequent delivery by either the vaginal or abdominal route is certainly not more hazardous than vaginal delivery in the presence of complicated fibroids or cesarean section followed by myomectomy or hysterectomy. Furthermore fibroids which have shown any evidence of change during pregnancy are notorious for the high incidence of morbidity during the puerperium—such complications in their order of frequency being hemorrhage, infection, and degeneration. Therefore the fibroid that shows evidence of pathology during pregnancy should be removed either during the pregnancy or at the time of delivery. To permit a patient with such a fibroid to deliver by the vaginal route and to disregard the presence of such a fibroid is to court disaster.

Polaks believed that myomectomy should be performed during pregnancy when fibroids are incarcerated, when they are growing rapidly, or when the subserous pedunculated type becomes twisted. Mussey and Hardwick[1] add to these indications "serious symptoms of degeneration" and in their series of 32 myomectomies performed during pregnancy, 21 were removed for this indication. Mayer[9] agrees

with these indications and states that "myomectomy is not only safe but frequently actually saves the child and preserves the pregnancy." Kosmak[11] advocated the removal of any fibroid showing evidence of necrosis.

Mayer offers the following recommendations: (1) that the uterus be handled as little as necessary; (2) that if possible the myomectomy be done with the uterus in situ rather than to attempt an eventration or excessive handling during the myomectomy. We are in hearty accord with such recommendations as well as those of Kosmak[10] who recommends, "laparotomy under deep anesthesia with enucleation of the growth and careful suture of the uterine wall . . . without extensive hemorrhage, abortion, or premature labor, if the patient is kept well narcotized after operation." We believe further that it is of the utmost importance to avoid the uterine cavity during the performance of myomectomy in pregnancy as we are convinced that the incidence of postoperative miscarriage rises in direct proportion to the incidence of uterine cavity invasion. Careful hemostasis is also necessary to insure a safe outcome of this type of operation. Continued oozing of cut surfaces or the formation of early adhesions to surfaces left raw and not peritonized will result in stimulation of the already irritable uterine musculature. Lastly, we believe in removal of only the guilty fibroid. In many instances fibroids are multiple and it is the natural tendency of the operator to want to remove all the significant fibroids which may be present. We believe this to be a serious mistake. Not only the patient but the pregnancy as well is much safer if the guilty fibroid alone is removed. Other intramural fibroids which may be present but which have given none of the indications for surgical interference such as acute degeneration, hemorrhage, infection or rapid growth, must be left undisturbed. This would obviously not hold for any subserous pedunculated fibroid of the uterus which may be present, since this latter type may be removed by simple ligature of the pedicle without adding further insult to the pregnant uterus.

We believe that the overwhelming majority of fibroids accompanying pregnancy require no treatment. The small group which shows evidence of acute degenerative changes, infection, hemorrhage, those pedunculated fibroids which undergo torsion, those which because of location "encroach upon" the birth canal, and finally those which undergo very rapid growth, should be removed during pregnancy. Myomectomy during the course of pregnancy should be done at the time indications arise and irrespective of the age of the fetus. Such a procedure obviates the necessity of cesarean section followed by myomectomy or hysterectomy, a more complicated procedure than myomectomy followed by subsequent vaginal delivery; also it obviates the danger of the puerperal complications which result so frequently when such fibroids are left in situ.

CONCLUSIONS

1. The indications for myomectomy are acute degenerative changes, hemorrhage, infection, twisted pedicle, or rapid growth together with encroachment upon the birth canal.

2. The recommended technique must include (1) minimal handling of the pregnant uterus; (2) the myomectomy with the uterus in situ if possible; (3) complete avoidance of the uterine cavity; (4) careful hemostasis and peritonization; (5) removal of only the guilty fibroid.

3. Myomectomy during pregnancy is a comparatively safe procedure for both the mother and the fetus and should be performed promptly whenever indicated.

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DISCUSSION

DR. LEROY A. CALKINS, Kansas City, Kan.—Dr. Reis has very carefully stated that he is recommending this operation only on the rare case which presents serious and alarming symptoms. His paper would have been more forceful and convincing had he been able to present in contrast many cases of fibroids for which operation was considered but upon which operation was not done because of a carefully made decision.

DR. EDWARD L. CORNELL, Chicago, Ill.—A fibroid that is not causing any complication and is located in the lower uterine segment or in the birth canal should, in my opinion, be left alone until the patient goes into labor. Most of them will rise out of the pelvis and not interfere with the course of labor. If, after a reasonable test of labor, that does not occur, you still have plenty of time to do a cesarean section and if necessary you can remove the fibroid.

Whenever the cavity of the uterus is entered during a fibroid operation in pregnancy, it is wiser to remove the pregnancy at the same time because most of these patients will miscarry. We might as well do a clean operation from above as to allow the patient to go into labor and perhaps rupture through the operative wound. The same principle holds where there is a large raw surface difficult to appose.

DR. REIS (closing).—A fibroid that in early pregnancy is embedded in the hollow of the sacrum under the promontory will not rise later in pregnancy when it has become even larger. I do not believe that the intraligamentous fibroid fixed by the broad ligament will rise. I do believe that in general Dr. Cornell is correct in emphasizing that fibroids should not be removed simply because they are present in the lower uterine segment.

STATISTICAL ANALYSIS OF ONE THOUSAND ABORTIONS*

JALMAR H. SIMONS, M.D., F.A.C.S., MINNEAPOLIS, MINN.

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THIS examination of the statistical data of one thousand abortions has for its purpose an addition to the sum total of statistics and the corroboration of existing data obtained under similar circumstances. The general feeling of unreliability of statistics may be expressed in the phrase "statistics may tell you anything, even the truth." Accuracy of the data of abortions is impaired, principally, by noncompulsory registration and the desire for concealment of the induced abortion by those who are morally concerned. Undoubtedly, many abortions of the so-called unintentional belong in the induced group; and are only re-classified through suspicion due to the severity of symptoms, serious complications or impending death. No one knows how many abortions are represented by delayed menses, by the untreated and by secret interruption. However, Taussig, with statistics available in this country and abroad, combines mathematics with skillful discernment to arrive at the conclusion that there are approximately 681,600 abortions yearly in the United States, with a maximum of 10,000 deaths.

The records of these cases are uniform. The histories and physical examinations are made by student clerks and interns, who are supervised and their work authenticated by residents and re-examined by the staff. The unreliability of abortion histories is the bane of accurate etiologic statistics, but definite attempt has been made to obtain accuracy. With few exceptions, the admittances are indigent people.

Comparative findings as to race cannot be given as the colored are only represented here by seven abortions, four spontaneous and three induced.

TABLE I. EVIDENCE OF INCREASING ABORTIONS

	MINNEAPOLIS GENERAL HOSPITAL	N. Y. CITY
1930	178	2313
1933	320 (full year)	5197
Increase	180%	270%

There is some evidence that abortions are on the increase. With a steady yearly increase to 1933, there were 1.8 times as many as in 1930. This is only slightly affected by the increase in population.

Religion seems to be no deterrent to induction of abortion, as the Catholic, under restriction, and the Protestant, with the more liberal

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

TABLE II. RELIGION

	TOTAL	SPONTANEOUS	SELF-INDUCED	CORRECTED	% TOTAL CORRECTED AND SELF-INDUCED
Protestant	698	419	250	29	40
Catholic	268	151	98	19	43
Jew	24	17	7	0	30
Other	5	4	1	0	0

Excludes therapeutic abortions

view, when the statistics are corrected accordingly to population, have about the same incidence. The Jew is considerably lower in incidence as an abortion case although, according to Kopp's statistics obtained from birth control applicants, the latter is in the highest bracket. Peculiarly, in our series very few gave no religious affiliation although the Minneapolis religious census shows nearly an equal number of religious and non-religious status.

TABLE III. SOCIAL STATUS

	ABORTIONS	SPONTANEOUS	APPR. %	SELF-INDUCED	APPR. %	CORRECTED	APPR. %	% INDUCED	% TOTAL IN GROUP
Single	123	37	30	60	50	26	20	69.9	12.3
Married	840	541	64	281	33	18	2	35.5	84.4
Widowed	12	7	58	4	33	1	8	41.1	1.2
Divorced	20	6	30	11	48	3	15	70.0	2.0

Excludes therapeutic abortions

In regard to social status, the married show almost eight times as many abortions but fewer self-induced and many less of the criminal. Sixty-nine and nine-tenths per cent of abortions in the single were induced, compared to 35.5 per cent in the married people, and as one would expect a high percentage of induction in the widowed and divorced.

TABLE IV. DURATION OF PREGNANCY

MONTH	SPONTANEOUS	SELF-INDUCED	CRIMINAL	% TOTAL
1	64	25	3	9.2
2	249	158	18	42.8
3	203	119	17	34.0
4	33	34	8	7.5
5	35	18	2	5.4
6	7	2	0	0.9

Excludes therapeutic abortions

For the period of gestation, 9.2 per cent of the abortions were under one month; 42.8 per cent were one to two months; 34 per cent were two to three months but sharply decreasing in number after the first trimester.

Table V shows the number and type of abortion in the age groups. More than twice as many abortion cases were in the age group 20 to

TABLE V. NUMBER AND TYPE OF ABORTION IN AGE GROUPS

AGE	TOTAL	SPONTANEOUS	%	SELF-INDUCED	CRIMINAL	INDUCED %
Under 15	0	0		0	0	
15 to 20	132	85	64	34	13	35
20 to 25	311	154	49	137	20	50
25 to 30	224	135	60	81	8	39
30 to 35	177	94	53	76	7	48
35 to 40	108	94	87	14	0	13
40 and over	43	29	67	14	0	32

25 years than 15 to 20 years of age, gradually decreasing in number with age. However, the percentage of spontaneous abortions was approximately the same, until after 35 years, when a marked increase was shown. Inductions were considerably more frequent between 30 and 35 years, increasing again after 40 years of age.

TABLE VI. RELATIONSHIP BETWEEN PARITY, TOTAL PREGNANCIES, AND ABORTIONS OBTAINED FROM HISTORIES (EXCLUDING PRIMIGRAVIDAS)

PARITY	CONFINEMENTS	NO. OF WOMEN	ABORTIONS (ALL TYPES)	TOTAL PREGNANCIES	% ABORTIONS
1	214	214	309	523	59.1
2	364	182	354	718	49.3
3	387	129	230	617	37.3
4	324	81	170	494	34.4
5	295	59	112	407	27.5
6	288	48	109	397	27.4
7	231	34	82	320	25.9
8	96	12	26	122	21.3
9 or more	171	19	54	281	19.2
Total	2370	778	1446	3879	

One abortion to 2.7 pregnancies
One abortion to 1.6 confinements

Table VI shows the relationship between parity, previous total pregnancies, and abortions as obtained from histories of these abortion cases. The primiparas show 59.1 per cent of the total pregnancies were abortions but a gradually decreasing percentage, as parity is increased. In the totals there is one abortion to 2.7 pregnancies and one abortion to 1.6 confinements but the relation of abortions to hospital confinements is 1:5.4, which is approximately the relation given by Williams, also Whitehouse, for abortions in all types of practice. "Plass and others indicate the relation of one abortion to 2.5 confinements in the cities and one abortion to 5 confinements in rural districts."

It is peculiar that the ratio of stillbirths to abortions in each of the four years of these records is approximately 1 to 5, averaging 1 to 5.2.

Table VIII indicates the methods used to induce abortion. Ergot and quinine were the drugs of choice and the catheter was used in about 87 per cent of the cases for self-induction and criminal abortion. Three deaths were questionably the result of external trauma, eleven by catheter or curettage, three following drug induction, which is doubtful, and two undetermined but suspectedly criminal.

TABLE VII. RELATION OF ABORTIONS TO HOSPITAL CONFINEMENTS AND STILLBIRTHS

YEAR	ABORTIONS	CONFINEMENTS	RATIO (AB.)	STILLBIRTHS	RATIO (STILLBIRTHS)
1930	178	1023	1:5.7	42	1:4.2
1931	262	1258	1:4.8	43	1:6.0
1932	317	1685	1:5.3	73	1:4.3
1933	320	1849	1:5.7	50	1:5.6
	Full year				
			Av. 1:5.3		Av. 1:5.2
Williams			Average		1:5.4
Whitehouse					1:5.9
Plass and others			Urban		1:2.5
			Rural		1:5.0

TABLE VIII. METHODS USED TO PRODUCE ABORTION

	METHOD	SELF-INDUCED	CRIMINAL	DEATHS
Drugs	Ergot	24		
	Quinine	32		2
	Purges	7		
	Female pills	4		1
	Undetermined	2		2
Instrumental	Slippery elm	7	2	
	Catheter	101	13	8
	Packing		7	
	Curettage		6	3
	Wire	4	2	
	Unstated	3	15	
	Suspected		3	
	Ext. trauma			3

The febrile cases (Table IX) comprised 18.9 per cent of the spontaneous abortions, 36.9 per cent of the induced. Eighty-one per cent of the spontaneous were afebrile and 63.1 per cent of the induced. From inaccuracies of history, undoubtedly some of the spontaneous cases belong in the induced group, but it is a clinical fact that in the absence of interference ascending infection and sapremic manifestations give much the same picture until the abortion becomes complete. In the latter, the phenomenon is an immediate drop in temperature to normal; in the latter, often, by lysis.

TABLE IX. TEMPERATURES IN ABORTION CASES

	SPONTANEOUS	%	SELF-INDUCED	CRIMINAL	%
Afebrile	479	81.0	227	28	63.1
Febrile	112	18.9	129	20	36.9

Excludes therapeutic abortion
Afebrile, below 100.4° F.

Table X shows the degree of hemorrhage. Rarely does a patient who has had an abortion die of hemorrhage and that is true of this series, although 3 were exsanguinated.

Excluding therapeutic abortions, approximately 5.9 per cent of the patients were readmitted (Table XI), 2 patients for infection and 57

for hemorrhage. Over one-half of these had retained secundines; the remainder returned for menorrhagia, metrorrhagia, infection, or subinvolution.

TABLE X. ABORTION HEMORRHAGE

HEMORRHAGE	NUMBER	PER CENT
Slight	40	4.0
Moderate	502	50.4
Profuse	450	45.3
Exsanguinated	3	0.3
No deaths from hemorrhage		

TABLE XI. ABORTIONS READMITTED

	NUMBER
For hemorrhage	57
For infection	2
Treatment	
Expectant	22
Curettage	37

TABLE XII. MISSED ABORTIONS (3)

PARITY	FETUS		RETENTION	WASS.	HB.	R.B.C.	W.B.C.	URINE	B. P.	OP. TR.
Multi.	14½ cm.	3.7 mo.	9 wk.	-	83	4,000,000	2,000	-	102/78	0
Multi.	15½ cm.	3.9 mo.	16 wk.	-	102	4,500,000	7,500	+ Alb.	146/78	0
Multi.	5½ cm.	2.5 mo.	12 wk.	-	89	Not taken	6,500	-	105/55	Curettage

There were three missed abortions in the whole group, one under three months and two over three months. One showed minimal signs of toxicity by slight albuminuria and a rise in blood pressure. Two were spontaneous, the other evacuated with a sponge holder.

Five therapeutic abortions were done for the following indications: chorea, decompensated heart, endocarditis, incipient tuberculosis and

TABLE XIIIA. THERAPEUTIC ABORTIONS (5)

PARITY	DURATION	INDICATION	MORTALITY
1	3 mo.	Chorea gravidarum	0
3	2 mo.	Mitral insufficiency and stenosis Decompensation	0
1	2 mo.	Incipient T.B.	0
1	2½ mo.	Carcinoma of bowel	0
1	2 mo.	Recurrent rheumatic fever Endocarditis	0

TABLE XIIIB. MORTALITY

GESTATION	SPONTANEOUS	SELF-INDUCED	CRIMINAL
Under 3 mo.	2	12	2
3-6 mo.	1	2	0
6 mo. and over	0	0	0
Mortality	1.9 per cent		

one for a pregnancy in a patient, who one month previously, had been operated upon for carcinoma of the bowel. There was no mortality in this group.

Table XIIIB shows a mortality rate of 1.9 per cent.

Table XIVA shows the clinical data of 19 abortion deaths, a mortality of 1.9 per cent. All were under 35 years of age, 4 were nulliparas and 15 had previous abortions, 4 of which were spontaneous, 13 self-induced, and 2 criminally produced.

Table XIVB shows that 7 gave no history of chills, 3 an initial chill, and in 9 the rapidly lethal, repeated chills. Clinically, those cases with a low leucocyte count, rapidly depreciating blood and repeated chills are most ominous. Blood cultures were positive in 37 per cent; all were cultured at autopsy, showing the following organisms in the blood of 63 per cent or 12 cases—*Streptococcus viridans* and *hemolyticus*, staphylococcus, colon bacillus and in one case *Bacillus welchii*.

In Table XIVC are given the other complications, the most frequent of which were peritonitis, infarcts, phlebitis, and pneumonia.

TABLE XIVA. CLINICAL DATA ON NINETEEN ABORTION DEATHS

Age	25 yr. or less	10 cases
	25 yr. to 30 yr.	7 cases
	30 yr. to 35 yr.	2 cases
Parity	Nullipara	4 cases
	1 viable birth	1 case
	2 viable births	5 cases
	3 viable births	5 cases
	4 viable births	4 cases
Previous abortions	1	7 cases
	2	6 cases
	3	2 cases
Type of abortion	Spontaneous	4 cases
	Self-induced	13 cases
	Criminal	2 cases
Hemorrhage	Slight	12 cases
	Moderate	5 cases
	Profuse	2 cases

TABLE XIVB. CLINICAL DATA ON NINETEEN ABORTION DEATHS

Chills	None	7 cases
	Initial	3 cases
	Repeated	9 cases
Temperature	102-104°	4 cases
	104-106°	8 cases
	106-109°	7 cases
Leucocyte count	to 13,000	9 cases
	14 to 20,000	6 cases
	21 to 30,000	2 cases
	34,000	1 case
	55,000	1 case
Hemoglobin	30-50	2 cases
	50-70	4 cases
	70-90	7 cases
	90-95	5 cases
	Not recorded	1 case

TABLE XIVC. CLINICAL DATA ON NINETEEN ABORTION DEATHS

OPERATIVE PROCEDURES	COMPLICATIONS (AUTOPSIES—ALL DEATHS)	
Colpotomy—1	Septicemia 63% or	12 cases
Incision parotid abscess	Peritonitis	11 cases
	Endometritis	13 cases
	Pneumonia	9 cases
	Endocarditis	5 cases
	Lung infarct	2 cases
	Lung abscess	1 case
	Infarcts kidney and spleen	2 cases
	Acute hepatitis	1 case
	Kidney abscess	1 case
	Empyema	1 case
	Edema of lungs	1 case
	Toxic myelitis	1 case
	Brain abscess	1 case
	Pelvic cellulitis	1 case
	Thrombophlebitis	
	Pelvic	7 cases
	Ext.	5 cases
	Self-perforation with gas bacillus infection	1 case

TABLE XV. OPERATIVE TREATMENT

Nonoperative	623
Evacuation	258
Curettage	95
Abdominal incision for parametrial abscess	3
Posterior colpotomy	3
Transfusion	88
Operative incidence (excluding transfusions)	51%

Table XV shows the operative incidence in all cases. Evacuation refers to removal of decidua with sponge holder, finger, or both.

SUMMARY

1. One thousand cases of abortion are reported.

2. There is evidence of increasing number of abortions, principally in the self-induced group.

3. Religion does not seem to be a deterrent to induction of abortion.

4. As Taussig states, "abortion is a problem concerned with the married woman," both induced and criminal, and it is in this group that the high death rate is contained.

5. Most spontaneous and induced abortions occur under three months and most often under 30 years of age, increasing again in incidence after 35. The criminal abortions occur in greatest percentage in single women and early married life.

6. The total abortion incidence is 1 abortion to 2.7 pregnancies and 1 abortion to 1.6 confinements. This is according to the histories of our abortion cases. The relation of hospital abortion to hospital confinements is as 1:5.3 and stillbirths to abortions as 1:5.2.

7. Hemorrhage is a factor in lowering the resistance of the patient but not in the mortality.

8. Missed abortions were of 0.3 per cent incidence; therapeutic abortions 0.5 per cent.

9. The mortality rate was 1.9 per cent with the most frequent complications septicemia, peritonitis, pneumonia, phlebitis, and distant infarcts.

10. Operative incidence 51 per cent.

11. We have followed the conservative treatment established, here by Adair and Litzenberg, that is, in septic cases, we use expectant treatment unless complicated by hemorrhage; incision of abscesses if properly located, later evacuation if necessary when there is approximately normal leucocyte count and temperature for a period of at least five days. The sedimentation time does not seem to be of much value here. Nonseptic cases are evacuated, almost routinely, to conserve blood and shorten hospitalization. Repeated transfusions are of particular value in infected cases, and of course those with hemorrhage. Nearly all cases with a hemoglobin of 60 per cent or less received one or more transfusions. Sulfanilamide seems to give promise of potent therapy.

12. Invalidism, more or less permanent, and the high maternal mortality of abortion may hopefully be combated through improvement in moral and economic standards, education in family limitation, and early prenatal care. Endocrine and vitamin therapy may eliminate many of the spontaneous abortions.

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DISCUSSION

DR. RALPH R. WILSON, Kansas City, Mo.—Abortions is a title that relatively few wish to use for a presentation because of the undercurrent of feeling that it is a delicate subject of a slightly unsavory nature. Not only is this far from the fact, but so long as abortions play such an important part in maternal morbidity and statistics, it is necessary that such an organization as ours devote a part of its program to discussions of this subject regularly.

The staff of the Minneapolis General Hospital is to be commended on the exceptionally noteworthy manner in which these cases have been cared for. The low mortality rate is no accident. In my brief search for a comparable series I have found only one that was better than the 1.9 per cent reported here. A smaller series by Dr. T. K. Brown of the St. Louis City Hospital has a trifle better than average death rate. Especially noteworthy in the above report is that there are no deaths from hemorrhage.

In order to emphasize the importance of Dr. Simon's conclusions and to accentuate his results I desire to refer to a statistical study of 1,200 abortion cases handled in the Kansas City General Hospital between the years 1923 and 1933 inclusive.

1. The Kansas City series had an incidence of 25.3 per cent of septic cases as compared to 18.9 per cent in the Minneapolis cases.

2. Death rate in the Kansas City series was 3.6 per cent as compared to 1.9 per cent for Minneapolis.

3. Each city had one case due to *Bacillus welchii* and lesions in the uterus were obtained from an autopsy of the Kansas City case.

4. Hemorrhage caused no deaths in the Minneapolis series while in the Kansas City series, four died from hemorrhage.

5. Conservative, supportive, and symptomatic measures were the characteristic modes of treatment in both institutions.

DR. RUDOLPH W. HOLMES, Chicago, Ill.—Dr. Simons reiterates a statement I have constantly declared, namely that religion, social status, education, etc., are no deterrents to a woman who desires to get rid of her pregnancy. I believe that in

proportion to the number of full-term deliveries, married women have a higher rate for abortion than the unmarried.

Operations have a very small place in the routine care of an abortion, whether it be a spontaneous termination of pregnancy or a criminal interruption. The one and outstanding indication for obstetric interference in an abortion is hemorrhage. Curettage in the presence of infection merely "throws gasoline on the fire": I would recall to you that Bumm's "reaction zone" is nature's attempt to limit the spread of infection, instrumentation in the uterus destroys that protective zone. The infected uterus is, in fact, a draining abscess cavity, and what surgeon would curette an abscess wall!

My own conviction is that abortions, induced by a second party or by the woman herself, exceed in incidence those resulting from all pathologic causes, or accidents. Some women blatantly will discuss their criminal interruptions, but most will deny such aid to their dying breath. This evasion plays a dominating part in the history of abortion in private practice as well as in institutional care. Any statistical study will but intimate the frequency of induced abortion.

DR. CHARLES E. GALLOWAY, EVANSTON, ILL.—The figures we have heard this morning came from large county hospitals, dealing with the undercared-for and mishandled cases among indigent people who have not taken proper care of themselves. I would like to give a brief comparison with statistics of abortion based on an intelligent group of women who know how to take care of themselves.

At the Evanston Hospital, over a ten-year period, there were 778 cases of abortion—where the pregnancy was less than twelve weeks. There were four deaths in the 778 cases. One was of the criminal type in a patient who died after two months; one was an incomplete abortion in a patient who came into the hospital in shock; one was a criminal abortion in a patient who had conservative treatment; the fourth was a therapeutic abortion done for cardiorenal disease. Four deaths out of 778 cases leave a mortality of just a little over one-half of 1 per cent.

We operated upon a little over 65 per cent of these patients. When a patient with an incomplete abortion is bleeding profusely and we know that it is a non-infected case, we are prone, if the cervix is a little dilated, to evacuate the uterus. The patient is home in five days and out again in ten to fourteen days. One hundred and thirteen of these were complete abortions when they entered the hospital. Our incidence of abortion at the Evanston Hospital runs about one to eleven deliveries. In our private practice, including the ones that spontaneously abort at home, it runs one in nine. I do not think that any infected case should be handled operatively, but I am also of the opinion that too much conservatism leads to just as much infection of the birth canal as too little.

DR. J. L. BUBIS, CLEVELAND, O.—I was rather surprised when Dr. Simons mentioned that the abortion patient is examined by the intern, then by the resident, and then by the visiting surgeon. We found years ago that many cases that would not have had a spreading infection, developed it after so much manipulation. According to our routine, when an abortion case comes into the hospital, no examination is done, especially if it is possible that it might be an induced one. The patient is put to bed, treated conservatively with ice bags over the lower abdomen, and pituitrin is injected intramuscularly two or three times a day. The head of the bed is raised. Except in the presence of active hemorrhage, we do not examine these women for at least twenty-four to forty-eight hours. If at the end of that time the temperature and the white count are normal, then the question of emptying the uterus arises.

I think we traumatize the uterus more by trying to do a finger curettement than by using a large curette. If you use pituitrin first, there is no danger. The pituitrin helps to loosen the products of conception, to thicken the uterus, and to decrease the amount of bleeding. We have practically never perforated a uterus by this method.

There is one case I would like to report. This woman, a nurse, two months pregnant, had undertaken to induce herself under the strictest aseptic care. At the time of curettement the products of conception were removed, but the uterus found to be retroverted. A week after the curettement inasmuch as she had had a con-

tinuously normal temperature, we thought we would try to put the uterus up in position. Just a slight manipulation in bed caused some pain and we desisted immediately. The temperature rose to 105° F. that evening and within three days she was dead of a streptococcic peritonitis.

DR. GEORGE F. PENDLETON, KANSAS CITY, MO.—I would like to question the use of pituitrin in a potentially infected case. When the uterus contracts you push infection both ways.

DR. J. L. BUBIS, CLEVELAND, O.—We have considered that question of whether pituitrin might not force infection into the broad ligament or through into the lymphatics. Although we have been using it for twenty years, we have never had a case where we felt the use of pituitrin before emptying the uterus had caused any further damage.

DR. SIMONS (closing).—I agree with Dr. Pendleton that pituitrin and ergot, especially the former, might be harmful by inducing too much activity of the uterine muscle and thereby breaking down the leucocytic barrier in infected cases.

Dr. Bubis spoke about the danger of frequent pelvic examinations in infected cases. Although we use these cases for teaching purposes, we do not permit too frequent examinations.

THREE HUNDRED CASES OF EXTENSIVE CONIZATION OF THE CERVIX*

WITH FURTHER REPORT ON USE OF A SPECIAL ELECTRODE

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IN 1927, Dr. Mortimer Hyams, in an article entitled, *A New Instrument for Excision of the Diseased Endocervix,* described a method of coning out the endocervix by means of a special electrode designed by him, to be used with a cutting current. It is entirely due to his persistent and painstaking effort that this method has now become recognized as one of the best methods of treating most cases of chronic cervicitis. Hyams stated that his technique was not applicable in cases of marked eversion, for which the Sturmdorf operation was still the treatment of choice.

In 1932, the senior author (R. J. C.) began using the Hyams electrode for conization in cases of chronic cervicitis. Before long it became evident that, although this electrode worked well in nulliparous cases and in cases of mild cervicitis, it was not satisfactory for use in the more extensive cases, because the cutting wire on the electrode was too close to the central silicon tube to permit the removal of all of the infected tissue. In order to overcome this difficulty there was a need for a different type of electrode, and the development and

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

use of this new electrode was reported by the senior author (R. J. C.) in February, 1935. Three sizes of the electrode were made (Figs. 1, 2). It was felt that this electrode should be called a modified Hyams, as it is an electrode for extending the application of the principle of the hemostatic cutting current in the cervix, but in his articles Hyams states: "Conization has for its object eradication and destruction of diseased endocervical mucous membrane and its contained glandular structure, and this is accomplished with preservation of the underlying muscle as well as the uninvolved tissue," and further, "The instrument used must conform to the anatomical contour and length of

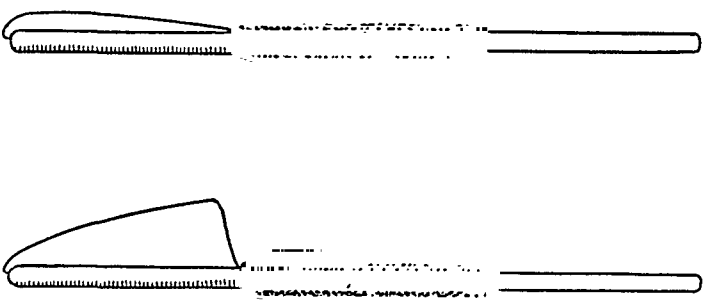
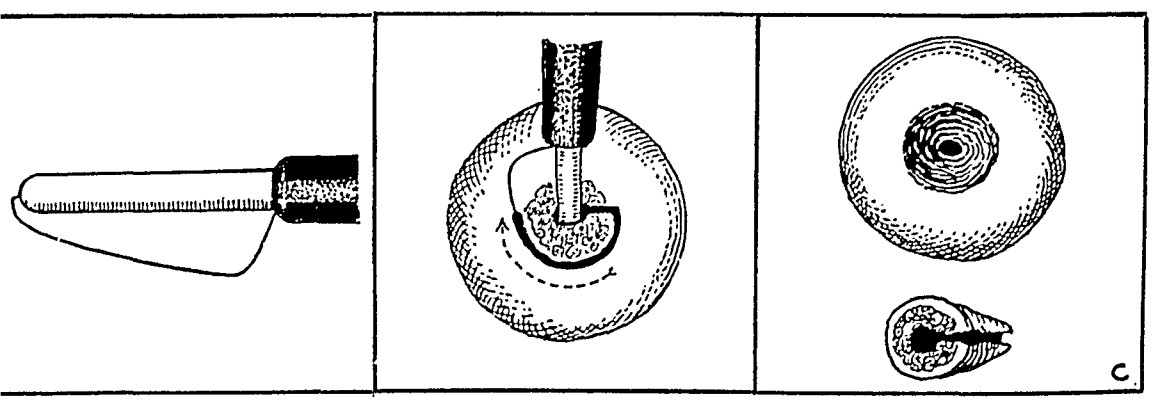


Fig. 1.—Upper electrode a Hyams, wire is one-eighth inch from the central core. Lower electrode is a medium-sized Crossen used for the wide conization to include all of diseased tissue.



A. *B.* *C.*

Fig. 2.—*A*, new electrode for wider conization; *B*, indicating method of using electrode, i.e., a wide excision taking in all of the affected area; *C*, the excised cone of tissue, and the remaining funnel-shaped cavity, which heals rapidly with good inversion. Crossen and Crossen—*Operative Gynecology*, Ed. 5, The C. V. Mosby Co., Fig. 293-1-5.

the cervical canal and the histological character of the lining membrane which is one-eighth inch in depth and rests on the basement membrane. Modifications of the Hyams electrode have been devised which do not duplicate the original specifications."

Dr. T. K. Brown in 1934 greatly improved the durability of this new electrode by two modifications. Instead of using the fragile silicon central core, the modified electrode has a brass tube covered with a hard rubber insulating material which is almost unbreakable. The other improvement is that the cutting wire is so arranged that it can

be easily and rapidly replaced, thereby eliminating the necessity of sending the electrode to the factory for repairs (Fig. 3).

In this paper we wish to report the results of 300 additional cases of extensive conization done since the 1932 and 1935 series and give the conclusions from our further study in this work. The patients were operated upon by 12 members of the visiting staff of Barnes Hospital and 9 members of the house staff. The series comprised both private and ward cases. The ward cases were followed after operation in the Out-patient Department and follow-up information on the private cases was obtained directly from the physicians who did the work. The three questions which were asked were: (1) Was there any abnormal postoperative bleeding? (2) Were there any cases of postoperative stricture? (3) Were there any pregnancies following conization? If so, describe any difficulties experienced with the pregnancy or delivery.

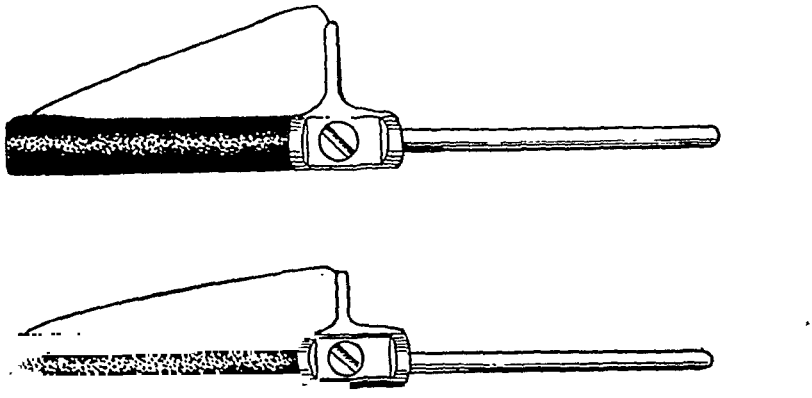


Fig. 3.—T. K. Brown modification of Crossen electrode. The unbreakable central core and replaceable cutting wire increase the durability of the electrode and reduce repair costs.

The procedure was carried out in combination with curettage and radium therapy, vaginal plastic operations, and abdominal operations.

Table I shows a summary of the operative procedures.

It is evident from this table that a sufficiently large number of cases have been done in combination with the various procedures mentioned to show that these combinations are not harmful to the patient. Conization offers a rapid efficient method of caring for the cervix in two types of cases. First, in cases of supravaginal hysterectomy where the cervix shows a mild cervicitis which is not extensive enough to warrant the additional strain of a complete hysterectomy, and second, in patients with a bad cervix where operative difficulties, or the patient's condition, contraindicate its removal. We have experienced no difficulty in doing the conization, following the abdominal operation, and we prefer to do it last because we feel that the more important, namely the intra-abdominal work, should be finished first, and then if for any reason further operative work is contraindicated the conization can be done later before the patient leaves the hospital.

TABLE I

Total number of cases		312
Routine conization		214
With suture		98
Lateral		37
Sturmdorf		68
Anterior and posterior	63	
One suture only	5	
Combination Lateral and Sturmdorf		7
With radium therapy		25
Sturmdorf suture	19	
No suture	6	
With abdominal operation		77
Supravaginal hysterectomy	19	
Other	58	
With vaginal operation *only*		31
With vaginal and abdominal operation		8
Coagulation of bleeders		22
T-tube left in cervix		12

RESULTS

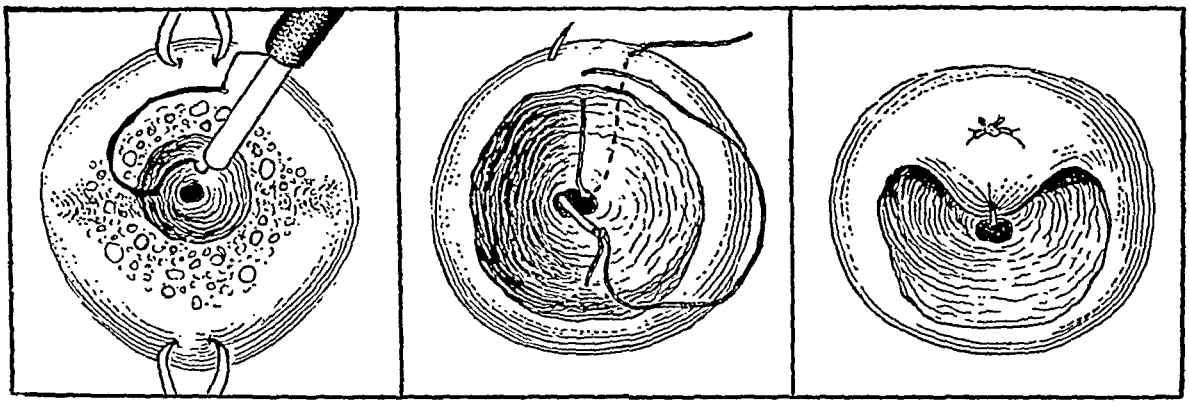
In most cases the cervix healed completely in three to four weeks, but in a few there were complications of bleeding or partial stricture. These are shown in Table II.

TABLE II

Total number of cases of bleeding		17
Wide routine (should have been sutured)	9	
Coagulated	2	
Conization in the premenstrual period	3	
Bleeding occurred with removal of radium	1	
Medium conizations with no explanation for bleeding	2	
Stricture		1

This table brings out several important points, the first being the choice of time for performing conization. Early in the work, we found that when the conization is done just before the menstruation, the ensuing period is frequently more profuse than usual and is prolonged. The premenstrual congestion throughout the pelvic organs is no doubt responsible for this fact. Since 1935, we have emphasized the importance of having the patient come in for conization immediately after the period so that the cervix will have about three weeks in which to heal before the onset of another period, and in this series the majority of cases were done in the postmenstrual period. We feel that this has been an important factor in the prevention of postoperative bleeding. In the table we see that three of the 17 cases having postoperative bleeding, had the conization in the premenstrual period and one of these cases was done only two days before the onset of the flow. The second point that we feel is very important, is the proper use of sutures. In 1935, when we first began to combine the suture with conization, we felt definitely that from a surgical standpoint it did not seem logical to suture the coned surfaces or to turn them in with Sturmdorf sutures, but as we had tried a few, and the cervices

had healed satisfactorily, we were encouraged to continue. In the present series of 312 cases, sutures were used in combination with conization in 98 cases. In the sutured cases there were only two instances of bleeding; one was in a case done premenstrually and the other occurred in a case where radium was used and evidently the wound was opened when the radium was removed. From our experience since 1935, we feel that sutures should always be used in the following types of cases: (1) Wide conizations where there is a good deal of eversion, regardless of whether they bleed at the time or not. (2) When there are bleeders at the time of conization. (3) When the radium or a stem pessary is used. The Sturmdorf suture has been found to aid the inversion and prevent late bleeding. If the eversion is marked, lateral Sturmdorf sutures can be used in combination with the anterior and posterior Sturmdorf suture (Fig. 4). In these cases



A. *B.* *C.*

Fig. 4.—Very extensive conization, with use of Sturmdorf suture to aid inversion during healing. *A*, the second round of tissue excision using medium-sized Crossen electrode is shown; this could have been done in one rotation using the largest size electrode. If the medium size only is available, excision is accomplished by making two rounds with the electrode. The second round is made well beyond the edge of the involved tissue so as to preserve its junction with the normal tissue for microscopic examination; *B*, passing the Sturmdorf suture in the anterior lip; *C*, the first suture tied, showing the inverting effect. This also shows the open area left at each side, giving plenty of drainage opening for each flap. For hemostatic effect, the entrance and exit of the Sturmdorf suture should be separated about twice the distance shown in *B*. An additional Sturmdorf suture may be placed wherever needed for good inversion or hemostasis.

we usually leave a Dakin tube in the cervical canal until the patient goes home, just as we do in an ordinary Sturmdorf operation, to prevent stricture. The use of the suture has allowed us to cone the more extensive cases of cervicitis, the type we used to feel needed the regular Sturmdorf operation, so that we now use the Sturmdorf operation only in cases requiring plastic repairs because of tears into the parametrium. The conization prevents most of the troublesome bleeding at the time of operation and the removal of the infected tissue is done more easily with the electrode than it is with the knife, so that the time required is shortened.

In Table II there are nine cases of wide conization without suture. We feel that, had these patients been sutured at operation, the bleeding would have been prevented. When there are bleeders even in a

case of moderate conization, we feel that it is better to suture and definitely stop the bleeding than it is to coagulate or pack. Our reasons for this are that with coagulation there is a tendency to have late bleeding when the slough separates and with a pack the gauze sometimes does not control the bleeder and if it does control the primary bleeding, it is likely to stick to the conized area and stir up bleeding when removed. In regard to stricture in the present series there was only one definite stricture and that was in a case of wide conization with Sturmdorf sutures, but no Dakin tube was used in the cervix. There were three other cases in which the operators stated that there was a *tendency* to stricture and hence the cases were dilated postoperatively in the office.

All but three of the postoperative bleeding cases were controlled by packing. The three requiring secondary sutures were wide conizations which should have had a primary suture. One of these cases was coagulated at the time of the conization, and was sutured for bleeding twenty-three days later. The other two were sutured on the first postoperative day.

In patients who bleed after conization, care should be taken to determine the source of the bleeding. It must be remembered that the operation is not infrequently done in patients who have irregular periods; in our series some of the cases would have been reported as bleeding from the conization had not the cervix been examined and found to be healed. The bleeding in these cases was coming from higher in the uterus.

The final question which was of interest to us was what happens during pregnancy and labor in these cases.

TABLE III

Total number of cases of pregnancy	15
These occurred in twelve patients.	
Delivery full term, all easy deliveries	5
Now pregnant, two to seven months	3
Miscarriages, six weeks to seven months	7

Of the miscarriages: One was at six weeks, two at two months, three at three to four months, and one at seven months. The miscarriage at seven months occurred after spontaneous rupture of the membranes and the child was born alive but died in a few hours. One of the remaining six miscarriage cases had a four-plus Wassermann and another was a diabetic. One of this group had a missed miscarriage almost three years after the conization.

Whether the conization was a factor in causing any of these miscarriages we are unable to give an opinion, as we have too few cases, and the conditions interrupting the pregnancies have not been investigated thoroughly. Most of these patients have had children and some of them are past forty. We hope that in the future the histories will include more details in these patients who abort, so that the cause

relationship to conization, if any, can be determined. The woman who miscarried at seven months is now six months pregnant. One of the patients who was delivered of a full-term fetus had had a spontaneous abortion previous to the conization.

Finally we would like to add that two unsuspected carcinomas were found in this series, while two suspected cases that had conizations done, also proved to have carcinoma.

SUMMARY

1. Conization of the endocervix by means of a special electrode to be used with a cutting current, originated by Mortimer Hyams in 1927, marks a distinct advance in the treatment of chronic cervicitis.

2. Extension of conization to include cases of extensive chronic cervicitis was effected through the use of a special electrode devised in 1932 by the senior author (R. J. C.), and 80 patients thus treated were reported by him in 1935. The durability of this electrode was greatly increased by T. K. Brown in 1934, by substitution in materials used.

3. Conization of this extensive type should preferably be done in the postmenstrual period so as to allow three weeks for healing before the onset of the following period.

4. The use of the Sturmdorf suture anteriorly and posteriorly and laterally if necessary, has allowed us to use conization in the more extensive cases of chronic cervicitis where the Sturmdorf operation was formerly the one of choice. It is better to suture any bleeders after conization rather than coagulate them.

5. Strictures should not occur in conization cases *if deep coagulation is avoided.* A small rubber tube should be left in the canal for seven days in the more extensive cases.

6. Postoperative bleeding in conization can practically be eliminated by the proper selection of time for operation and the use of sutures when indicated.

7. There have been no difficulties encountered in the delivery of patients who had had previous extensive conization.

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University Club Building

THE EFFECT OF ALKALINE VAGINAL DOUCHE ON THE HUHNER TEST AND STERILITY*

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FOR some time the method of procedure in the diagnosis and treatment of sterility has been rather definitely set down. While disappointments greet the steadfast, few indeed who step aside from the well-established routine ever reach the goal of solution. The beginning of this plan of attack is a carefully taken and analyzed history; the second step is a thorough physical examination in which must be included a study of cervical and vaginal reaction, and a careful "spermatozoa" or "Huhner" test. It is the study of these latter points with which our present paper is concerned, so further steps will not be recalled.

If vaginal and cervical secretions are not and cannot be made compatible with sperm life, then further steps are wasted time and effort, unless recourse is had to that most unsatisfactory procedure, artificial insemination. Fortunately, incompatible secretions often may be rendered compatible by the correction of infections and erosions, or by dilatation and curettage, or the alteration of vaginal chemical reaction. Possibly the procedures described by Roblee,[1] Adair and Hesseltine,[2] Hibbert and Falls,[3] in their respective methods of treating vaginitis and endocervicitis, by restoring the normal health of the cervicovaginal mucosa and establishing normal flora, may become the procedures of choice in correcting endocervical and vaginal incompatibility. The principal cause of sperm death and the unsatisfactory Huhner test is vaginal and cervical acidity, and the simplest and quickest method of attempting to establish conditions compatible with sperm life, even if only temporarily, is the precoital alkaline douche.

The use of the alkaline douche in the treatment of sterility is not a new therapeutic measure. It had been used long before Huhner[4] made his most outstanding contribution to the study of sterility, but its application has been, in most instances, as haphazard and half-hearted as the use of irrigations for leucorrhea before the more recent scientific discoveries determined the causes and thus made possible rational treatment.

Alkaline douches in the treatment of sterility are mentioned by Curtis,[5] Titus,[6] Traube and Weber,[7] Gray,[8] Loomis,[9, 10] Carey,[11] Cooke,[12] Berkow,[13] Rubin,[14] Dabney,[15] Meaker and Glaser,[16] Brinkley,[17] Watson,[18] Huhner,[19, 20] Bynsson,[21] Gibbons,[22] and others. Cooke[12] has given explicit instructions as to the strength of the douche, the time of application and the associated alkalinizing therapy. Byasson, quoted by Mann[21] in 1887, recommended injections with the following: Water, 1000 gm., the white of one egg, and 90 gm. of phosphate of soda. Our

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

results never had been in the least gratifying or even encouraging until our present procedure was adopted. Condom specimens never were entirely satisfactory in our hands, as Huhner[23] also recently states. The literature contains little that is explicit as to strength of solution or time of application, aside from the regime outlined by Cooke.[12] Unfortunately, the delay of a month by his method for study of a second Huhner test gives time for the family and the doctor to lose interest. Moreover, the late afternoon soda bicarbonate douche may have lost its effect in four hours. We have tested the pH of the vaginal secretions two hours and four hours after our irrigation and find it elevated at the end of two hours and again normal at the end of four hours.

TABLE I. CERVICAL AND VAGINAL pH UNDER VARYING CONDITIONS

NO.	pH ON FIRST EXAMINATION	ON FIRST HUHNER TEST NO PREPARATORY DOUCHE	ON SECOND HUHNER TEST WITH PREPARATORY DOUCHE
5542	Cervix 7.5 Vagina 5.0	Cerv. 7.5, rare motile sperm Vag. 7.5, many motile sperm	Cerv. 7.5, rare motile sperm Vag. 7.5, many motile sperm
5540	Cervix 7.5 Vagina 4.5	Cerv. 4.5, rare immotile sperm Vag. 4.5, rare immotile sperm	Cerv. 7.5, rare immotile sperm Vag. 7.5, few motile sperm
5550	Cervix 7.5 Vagina 5.0	Cerv. 7.5, many motile sperm Vag. 7.5, many motile sperm	
5541	Cervix 7.0 Vagina 5.0	Cerv. 6.0, no sperm Vag. 6.0, rare immotile sperm	Cerv. 7.5, no sperm Vag. 7.5, few motile sperm
5548	Cervix 7.5 Vagina 5.5	Cerv. 7.5, few motile sperm Vag. 7.5, many motile sperm	Cerv. 7.5, few immotile sperm Vag. 7.5, few motile sperm

The effect of the alkaline douche has usually been given as: first, neutralizing the acid vaginal secretions, and, second, dissolving the mucous plug from the cervix. A third and possibly more important effect, which to our knowledge has not been mentioned, may be the control of the pH titer in a range which favors the lytic action of the semen on the cervical mucus, the existence of which with its variations has been demonstrated by Kurzrok and Miller.[24] Our very limited observation of the vaginal and cervical pH under varying conditions would bear out this idea, and with further observations, this should be subject to proof (Table I*).

TECHNIQUE

Our present method of application developed from ideas obtained in conversation with Dr. J. Hofbauer in regard to another problem. In attempting to produce an isotonic vaginal medium in the treatment of another condition, we observed while using a 2.4 per cent sodium bicarbonate solution, that sperm accidentally obtained in a vaginal specimen had greater motility than the postcoital specimen after our usual alkaline therapy.

As a result of this, we established our procedure of using routinely a 2.4 per cent sodium bicarbonate irrigation fifteen minutes before coitus in all cases where our first Huhner test shows feebly motile sperm, dead sperm, or no sperm. The irrigation is taken in the recumbent position at low pressure, and the patient is advised to move about in the erect posture immediately afterward so that the excess of retained solution may drain away. It is believed that by using this solution, after dilution with cervicovaginal and prostatovesicular secretions, an isotonic or nearly isotonic medium is obtained. The time of examination is from one and one-half to two hours after coitus. Rubin[14] recommended the isotonic

*Detailed observations as to case numbers, dates of examinations, comparative findings, etc., are omitted for lack of space.

solutions of Ringer or Locke as possibly being preferable to alkaline solutions, but he says, "This is better founded on theory than upon actual therapeutic experience."

RESULTS

In the past three years since the institution of this procedure, 29 cases showed unsatisfactory findings with the first and satisfactory or improved with the second Huhner test. Eight pregnancies have resulted with the continuation of the alkaline douche measure (Table II). Two pregnancies occurred in the month following cessation of alkaline treatment. One patient became pregnant probably before institution of the treatment, though it had been advised. Her second Huhner test was found satisfactory six days after she missed her first menses. Another patient with a twenty-one- to twenty-four-day cycle, menstruated on the thirty-fourth day, with severe cramps and excessive flow.

For purposes of study, numerous cases were recalled who had shown previously only unsatisfactory Huhner tests. Five of these reported and with the preparatory douche, their tests were satisfactory. None of these patients have become pregnant (Table II).

TABLE II. EFFECT OF 2.4 PER CENT SODIUM BICARBONATE PRECOITAL DOUCHE ON VAGINAL INCOMPATIBILITY

Cases in which Huhner became satisfactory after institution of preparatory douche	29
Cases where pregnancy occurred on institution of preparatory douche	8
Cases where pregnancy occurred probably before institution of douche but after its recommendation	2
Recall cases Huhner's test unsatisfactory in former alkaline therapy but satisfactory in this	5
Cases where 2.4 per cent sodium bicarbonate douche had an apparent inhibiting effect on sperm motility	2
Cases where sterility was not the problem but pregnancy occurred during use of 2.4 per cent precoital douche	11
Cases where sperm were weak, immotile or absent without and with precoital douche	5

Two cases were found where the preparatory douche seemed to inhibit sperm activity. One of these patients reversed the procedure and came for the first Huhner test, having taken the preparatory douche, and no motile sperm were found. After a second Huhner test with no previous preparation, there were many motile sperm and she later became pregnant, without further treatment. A companion case had a satisfactory first Huhner test and an unsatisfactory second test following the preparatory bicarbonate douche. These cases are the strongest argument against the frequent indiscriminate prescribing of the alkaline douche in cases of sterility without necessary evidence supplied by a double Huhner examination. We have checked this on a number of cases that showed a satisfactory first Huhner test, and we believe that the above finding is rare, but it must be considered. To further bear out the probable infrequency of the above-mentioned inhibiting effect of the bicarbonate douche on sperm activity, we have listed eleven cases in which pregnancy occurred while the preparatory douche was being used where sterility was not the problem (Table II).

Five cases showed unsatisfactory first and second Huhner tests. An unsatisfactory second Huhner test almost invariably means some defect in the male, so we have dispensed with asking for condom specimens, and refer the husband to a urologist for examination. In one case, this was refused; in another, the husband has been too busy to comply with our request; and in a third case, the husband was found to have bilateral undescended testicles. One husband showed improvement from a nonspecific prostatitis, and the wife, after cervical abdominal myomectomy, conceived. Another husband, under treatment for some months, has just been pronounced improved and probably potent. These and a number of the series of

twenty-nine exhibited considerable pus and debris on the Huhner examination. Huhner[4] has said that pus has little effect on fertilization, referring particularly to the pus of an acute gonorrhea, but Kurzrok and Miller[24] have shown that the presence of pus in the mucus plug of the cervix definitely lowers the lytic action of the semen, so it would seem advisable to treat as thoroughly as possible any infection, specific or nonspecific, in both members of the union in the endeavor to increase their fertility. One of this group of five patients where the husbands showed deficiency has been subjected to lipiodol visualization and dilatation and curettage without a preceding Huhner examination. In the group of twenty-nine patients who showed improvement with the bicarbonate douche, one had a lipiodol visualization, another a Rubin test without preceding Huhners in the hands of other examiners. Using the preparatory douche, one of these became pregnant and has been delivered. It would seem that these three patients had been subjected to procedures possibly unnecessary.

From the very limited study of the pH taken on first examination at the time of the first Huhner test, and at the time of the second Huhner test following a precoital douche, it is interesting to note that the alkalinity of an apparently normal semen elevates the pH of the vagina to the level of the pH of the cervix (Table I). Gray[8] has called attention to the fact that the alkalinity of the sperm will overcome the acidity of the vagina where the acid secretions are not too great in quantity. The findings in these limited observations would confirm his idea. It would seem also that the addition of the alkaline preparatory douche does not alter the degree of elevation of pH produced by normal semen, but assists in the pH elevation where the semen is not sufficiently alkaline to produce the desired alkalinity. It is well also again to mention here the work of Kurzrok and Miller.[24] These investigators have shown that the lytic action of semen on the cervical mucus plug exhibits its maximum activity in two ranges from pH 5.28 to pH 5.90 and from pH 7.37 to pH 8.04. The lytic action of normal semen is absent below pH 4.00 and above pH 10.00. Our readings for pH after the 2.4 per cent bicarbonate of soda douche with and without coitus stand at pH 7.5, within the range of maximum lytic activity.

SUMMARY

The action of the alkaline douche in the treatment of sterility is discussed. In twenty-nine cases where incompatibility existed, apparent compatibility was established by the use of a 2.4 per cent sodium bicarbonate douche taken fifteen minutes before coitus. Eight of these patients became pregnant.

It is pointed out that the 2.4 per cent sodium bicarbonate douche created a temporary incompatibility in two cases and the desirability of the double Huhner examination both with and without the preparatory douche, before recommending its use, is emphasized. The advisability of substituting the second Huhner test with a preparatory douche for the examination of the condom specimen, and the avoidance of further examination or treatment, medical or surgical, of the patient until potency of the husband and compatibility are established is suggested. A very limited study of the cervical and vaginal pH under varying circumstances is presented and would indicate that the alkaline preparatory douche is ordinarily not harmful to normally alkaline sperm and is beneficial to sperm not sufficiently alkaline to overcome vaginal acidity or hyperacidity.

CONCLUSIONS

1. The incompatibility of vaginal secretion with normal sperm activity as evidenced by the negative Huhner test may be overcome

quickly and efficiently in most instances by a 2.4 per cent sodium bicarbonate douche taken fifteen minutes before coitus.

2. Numerous cases of primary sterility may be relieved by the use of the 2.4 per cent sodium bicarbonate precoital douche.

3. The 2.4 per cent sodium bicarbonate precoital douche should not be used without the proof obtained by the double Huhner test that such a douche is not detrimental to sperm motility.

4. The double Huhner test is a rapid and efficient method of determining the possibility of establishing compatibility of sperm with vaginal secretions. Where this procedure fails, a general and urologic examination of the husband should be carried out before the wife is subjected to further medical or surgical measures.

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DISCUSSION

DR. CHARLES W. FROATS, St. Paul, Minn.—The use of precoital alkaline douches has hitherto been more or less haphazard, and herein we have a reassertion of the value of this procedure in the difficult problem of sterility treatment. Meaker, however, maintains that the alkaline douche is of no chemical importance and hence of little value in this phase of the treatment. Rubin recommends it particularly where there is a thick tenacious cervical plug. The normal alkalinity of the semen undoubtedly overcomes the vaginal acidity itself in many instances. Precoital douches of 5 per cent dextrose have been suggested as an activator of sluggish spermatozoa in preference to the alkaline douche.

The author does not state whether or not existing cervicovaginal conditions, such as bilateral cervical lacerations and erosion, Nabothian cysts and endocervicitis, were corrected prior to the use of this routine procedure. If so, this study has an increasing significance. Eight pregnancies, or 36 per cent, of 29 cases showing incompatibility, as indicated by the double Huhner test, is a commendable result and the authors are to be complimented upon their efforts.

DR. WM. T. BLACK, Memphis, Tenn.—Certainly, in those cases that have been previously treated by a deep cauterization, or an amputation destroying the Nabothian glands and eliminating the alkaline mucus from these glands, douches

should be especially indicated. Alkaline douches are also indicated where we have a lack of secretion from the Bartholin glands. Finally, alkaline douches in the absence of alkaline mucus should also be of benefit in cases of frigidity.

DR. SINGLETON (closing).—I have not used glucose solution in attempting to correct vaginal incompatibility. In my study, the bicarbonate douche has sufficed and in the great majority of instances has given completely satisfactory results in its correction. In some of these cases, cauterization was done, some had thyroid medication, some had correction of cervical lacerations and erosions, probably also influencing hyperacidity. It is interesting to note, in the patients who become pregnant on using alkaline preparations, that the pH was corrected. This would suggest that hyperacidity had been responsible for the incompatibility and had had an influence in inhibiting sperm so that pregnancy could not occur.

The question of increased alkalinization of the vaginal secretion at the time of coitus is of interest. It has been brought out by others that when orgasm occurs, there is a release of the alkaline cervical secretions into the vagina, increasing the pH so that the sperm will live and get into the cervix. Whether this is the mechanism or whether it is due to the alkalinizing effect of the normal healthy semen is uncertain.

PROPHYLACTIC ENDOCRINE THERAPY IN ARTIFICIAL MENOPAUSE*

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THE specificity of the estrogenic substances in the alleviation of menopausal disorders has been quite definitely established. Confirmation of clinical results has been provided by the work of Papanicolaou[1, 2] and Davis,[3] who have demonstrated by means of vaginal smears and biopsies of the vaginal mucosa, respectively, that adequate estrogenic therapy in menopausal disorders produces a return to normal of the vaginal mucosa accompanied by symptomatic relief, and that cessation of therapy is followed by regressive changes in the vaginal mucosa and recurrence of subjective symptoms.

In a previous presentation[6] before this Society, clinical data in a series of 85 cases were submitted as evidence of a syndrome suggestive of estrogenic deficiency. Subsequently 434 similar cases have received estrogenic therapy with the results as shown in Table I.

TABLE I. CLASSIFICATION AND RESULTS IN PRESENT SERIES OF 434 CASES

	NO. OF CASES	RESULTS OF THERAPY		
		SUCCESSFUL	FAILURE	INCOMPLETE
		RELIEF OF SYMPTOMS	PARTIAL RELIEF OR FAILURE	THERAPY NOT CONTINUED
Premenopausal	331	281	25	25
Menopausal	103	99	3	1
Total cases	434	380	28	26

*Read at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

Experience in 519 cases therefore would seem to indicate that when encountered in association with or prior to the menopause, any combination of the symptoms described in my previous paper must be given consideration as evidence of estrogenic deficiency.

Notwithstanding the excellent clinical results which have been reported by Sevringhaus[5] and a host of others, maximum efficiency of therapeutic measures has not been attained. This failure may be accounted for to some degree by our lack of an accurate concept of the varied symptomatology produced by estrogenic deficiencies of the menopausal type. One of the most confusing factors in the treatment of menopausal disorders has been that the term "hot flushes," probably one of the most frequent and disturbing symptoms of the menopause, has become synonymous with the term "menopause." As a result, absence of "hot flushes" has been accepted as indicating absence of menopausal disorder, and other symptoms or groups of symptoms equally severe and distressing, and persisting many years after cessation of the menses, have been ignored as an indication of estrogenic deficiency. Another disconcerting factor in therapy of this type has been the variation in therapeutic requirements. Since the introduction of estrogens of higher concentrations, it has been possible to obtain relief in a much larger proportion of patients and the variation in requirements which has been encountered in the present series of cases provides the explanation for failure of routine methods of therapy. Accurate determination of the requirements in each instance is essential before maximum relief can be obtained.

TABLE IIA. CLASSIFICATION OF 103 MENOPAUSAL CASES IN THE PRESENT SERIES

	RESULTS OF THERAPY		
	SUCCESSFUL	FAILURE	INCOMPLETE
Spontaneous menopause	55	3	1
Artificial menopause	44	0	0
	99	3	1

TABLE IIB. CLASSIFICATION OF 44 CASES OF ARTIFICIAL MENOPAUSE

		HYSTERECTOMY ONLY	PARTIAL OVARIAN ABLATION	COMPLETE OVARIAN ABLATION
Prophylactic therapy	21 cases	11	2	8 surgical
Late therapy	23 cases	10	2	11 { 7 surgical 4 x-ray and radium

Of the 434 cases in the present series, 103 were classified as menopausal patients as indicated in Table II. Of this number 55 were cases of spontaneous menopause of varying duration and severity of symptoms, while 44 were cases of artificial menopause resulting from surgery in 40 cases, radium in 3 cases, and x-ray in 1 case. Of the total of 44 cases of artificial menopause, 23 were cases of long standing while the remaining 21 represent the number in which various symptoms of the syndrome prior to operation were accepted as indications of estrogenic deficiency, and prophylactic therapy was instituted.

The difficulty encountered in securing and maintaining symptomatic relief in cases of long-standing menopausal disorder in contrast to the

ease with which complete relief may be obtained in the early cases, has been one of the most striking observations and suggested the possible advantages of prophylactic therapy. Recognition of the varied symptomatology as indicated in the syndrome and the frequency with which it has been encountered in many women in the complete absence of pelvic pathology was followed by recognition of the same symptoms in women having definite pelvic pathology. Almost immediate exaggeration of these subjective symptoms had occurred after surgical, x-ray, or radium therapy in 13 of the late cases of artificial menopause where partial or complete ovarian ablation had been necessary. This change was usually inaugurated by a stormy and prolonged convalescence followed by gradual transition of the previous symptoms to definite menopausal manifestations. In the remaining 10 cases where hysterectomy only was necessary, a more gradual but none the less definite increase in severity of menopausal symptoms was reported, substantiating the long recognized fact that even simple hysterectomy hastens decline of ovarian function.

Further observation and direction of history taking revealed that in most instances where pelvic surgery is necessary some of the symptoms submitted above as evidence of estrogenic deficiency may be elicited. In the 21 cases cited in which the need for operation was not immediate, preoperative estrogenic therapy administered as subsequently outlined resulted not only in relief of the symptoms but in definite determination of dosage in each instance prior to operation. Reinstitution of therapy as soon as possible postoperatively was followed by a marked decrease in the period of convalescence and in the 11 cases where ovarian integrity was not greatly interfered with, it was possible to maintain complete abeyance of symptoms with very low levels of therapy. Destruction or extirpation of ovarian tissue in the remaining 10 cases was followed in almost every instance by an increase in postoperative therapeutic requirements beyond those necessary prior to operation. Increase in therapy to the point of maximum symptomatic relief was necessary for about six months postoperatively in almost every instance before an equilibrium was established and reduction of dosage became possible. In no instance did any of the 29 patients develop the usual severe and distressing symptoms.

DETERMINATION OF THERAPEUTIC REQUIREMENTS

Previous observations[4] have established the fact that three types of reaction occur following parenteral administration of estrogenic substances. These reactions *occur within one hour after administration* and are of considerable significance though only transitory.

Reaction 1: Total absence of effect *within one hour* usually indicates that estrogenic deficiency exists and that the initial dose has been inadequate and should be increased.

Reaction 2: Improvement or relief of symptoms *within one hour,* or a feeling of well-being is evidence that an actual estrogenic deficiency exists and that therapy should be continued.

Reaction 3: Exaggeration of symptoms, extreme exhaustion, pain in the ovarian regions, or bearing down sensation *within the hour:* (a) if transitory and followed by relief of original symptoms, indicates that estrogenic deficiency exists but that dosage was excessive and should be decreased; (b) if prolonged and *not* followed by relief of original symptoms, the indication is that estrogenic deficiency does not exist and that therapy should be discontinued.

Determination of the dosage required in each instance was first obtained by intramuscular injection of amniotin in oil. Depending on the severity and duration of the symptoms, from 100 to 500 international units of Squibb's amniotin in oil were injected into the deltoid muscle. The patient was instructed to observe the effect within an hour and to report daily. The clinical response as outlined above was used as the criterion for increase or decrease of succeeding injections. The unit strength of the daily injections was increased until the minimal amount was ascertained which gave symptomatic relief for three to twelve hours. This dosage rarely exceeded 10,000 units and upon its determination the patient was placed on oral therapy in divided doses. If the parenteral requirements ranged from 1,000 to 10,000 units, oral therapy of 3,000 to 26,000 units of amniotin was given daily in capsule form (1,000 or 2,000 unit capsules). If the requirements ranged from 300 to 1,000 international units, an oral preparation of lower potency was indicated and the patient was placed on 150 to 800 biologic units of progynon (50 to 200 unit tablets). Daily requirements of 300 units or less indicated the presence of a very mild deficiency and Collip's emmenin was used in tablet or liquid form, giving either one tablet or its equivalent, 1 dram of the liquid preparation, three or four times daily. In those patients who obtained relief or manifested adverse symptoms with subsequent improvement with as little as 100 units of amniotin parenterally, complete symptomatic relief was obtained with as little as ½ dram of emmenin two or three times daily. When complete relief could not be maintained by oral administration alone, adequate amounts of amniotin in oil were given parenterally as often as necessary. When such additional therapy was required progressive decrease in frequency and dosage was possible until eventually symptomatic relief was maintained by oral medication only.

In the preoperative patient determination of dosage and symptomatic relief was usually accomplished within a week or two, thereby eliminating prolonged therapy prior to operation. Immediate reinstitution of the same dosage postoperatively has resulted in maintenance of freedom from previous symptoms and in a greatly improved convalescence. Following ovarian ablation the necessity for increase in therapy has occurred at any time within six months. Such increases have been indicated by recurrence of previous symptoms or by the appearance of other symptoms of the syndrome. Clinically, it had been previously ascertained that the symptoms produced by excessive therapy were as distressing to the patient as those resulting from lack of therapy. Any adverse symptoms developing after maintenance dosage has been established, except following ovarian ablation, have been due to the fact that the requirements of the patient have decreased and reduction of dosage

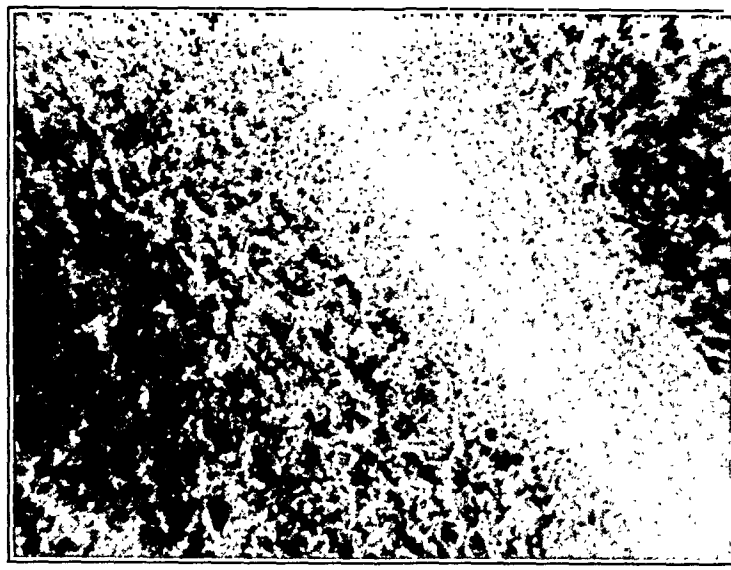
has been necessary. Under such circumstances the patient is advised to discontinue all medication for twelve to thirty-six hours. Relief of symptoms has been found to be an indication that the previous dosage was excessive and medication should be resumed immediately but with a decrease in amount. Conversely, exaggeration of symptoms following cessation of therapy indicates that the previous dosages have been inadequate and should be increased. The necessity for reduction of dosage continued until each patient was eventually placed on the liquid preparation of Collip's emmenin which in addition to being the mildest form of the estrogenic preparations available is best adapted for obtaining the small divided doses required in the later stages of the treatment. In almost every instance it has been possible eventually to reduce the dosage to one-half dram of emmenin once or twice weekly. Experience in the total series of cases has demonstrated that even at this point cessation of therapy is followed by recurrence of symptoms in from three months to one year. During the past two years, permanent therapeutic results have been maintained consistently in all patients who have continued on small dosage without interruption.

The above data are presented with full cognizance of the fact that relief of subjective symptoms does not always provide indisputable evidence. That such evidence is easily susceptible to the criticism that the results are due to psychic effect rather than physiologic action is recognized. With progress in this type of therapy, physiologic action has been definitely established by means of the vaginal smear method of Papanicolaou. It has also been of interest to note that repeatedly in the total series of 519 cases which form the basis for this presentation each case serves as its own control. Invariably maximum relief of symptoms has occurred only with exact determination of therapeutic requirements and in each instance any appreciable increase or decrease beyond these requirements has resulted in a return of symptoms while resumption of adequate therapy has in turn been followed by symptomatic relief. Further evidence of physiologic action is provided by the decrease in dosage not only possible but necessary in every instance.

CASE REPORTS

CASE 1.—May 20, 1938. Mrs. O., aged 43 years, had the menopause at age of 39, followed by exhaustion, nervousness, irritability, depression, leg-aches, hot flushes, perspiration, insomnia, frigidity, and spotting during past year increasing in past six months. Essential findings: blood pressure 170/84. Urethral caruncle, senile changes in vaginal mucosa, cervical erosion with flat polypoid areas on posterior lip of cervix which bled easily. Positive Schiller test. Uterus normal in size and position, some fixation. Inflammatory involvement of both adnexa. Therapy was begun on May 20, 1938. Determination of therapeutic requirements resulted in relief of symptoms with 0.5 drams of emmenin, t.i.d. Operation May 27, 1938: Abdominal panhysterectory (removal of all ovarian tissue was necessary). Convalescence was uneventful except for extreme exhaustion, hot flushes, excessive perspiration with severe backache starting on first postoperative day. Complete relief was obtained within forty-five minutes after administration of 300 units of amniotin in oil and maintained by 1 dram of emmenin, t.i.d. By August 7 recurrence of occasional hot flushes necessitated increase in therapy to 1 dram of emmenin, q.i.d., which was still giving adequate results on September 7.

CASE 2.—March 1, 1938. Mrs. S., aged 43 years, had a rupture of a chocolate cyst of the right ovary during intercourse twenty-four hours prior to operation. Operation: Bilateral oophorectomy, salpingectomy, and supracervical hysterectomy. The postoperative convalescence was uneventful except for extreme exhaustion and some



Figs. 1 to 7 show the histologic vaginal changes produced by estrogenic action under various conditions. Figs 1 to 3 indicate the rapidity with which these changes may be obtained by accurate determination of therapeutic requirements. Fig. 4 represents the complete effect of adequate estrogenic therapy, while Figs. 5 to 7 demonstrate the results of prophylactic therapy in artificially induced menopause. (Case 1.)

Fig. 1.—Vaginal smear in a typical case of spontaneous menopause prior to therapy. Extreme leucocytic infiltration, numerous basal cells and absence of cornified epithelial cells.

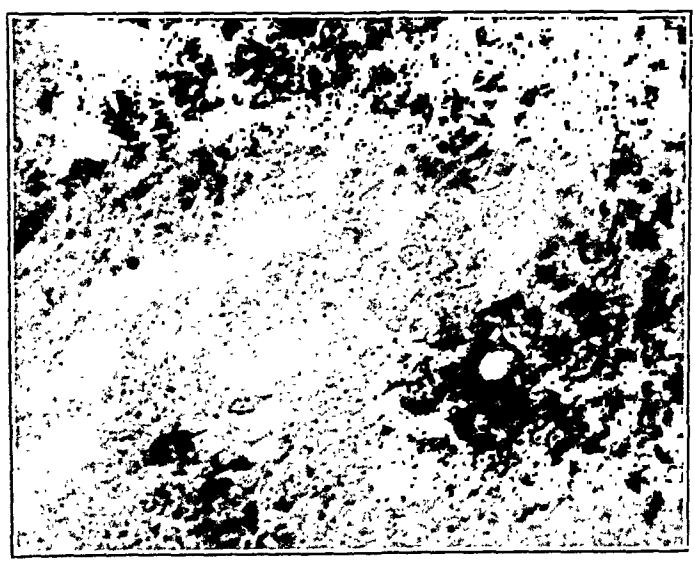


Fig. 2.—After parenteral administration of 500 and 1000 units of amniotin on succeeding days. Decrease in leucocytes and basal cells. Appearance of new squamous cell forms showing beginning cornification.

perspiration and feeling of heat. One tablet of emmenin, q.i.d., was sufficient to relieve symptoms at that time. By April 5 the emmenin was inadequate and hot flushes, extreme exhaustion, and insomnia had developed. Fifty units of progynon tablets, q.i.d., with amniotin in oil as an adjunct relieved symptoms until May 13 when further increase in therapy became necessary. This increase in therapeutic requirements

(5,000 to 7,000 units of amniotin) continued until August 31. Since that time it has been possible to maintain freedom from symptoms with 1 tablet of progynon, q.i.d., and amniotin in oil 2,000 units as required.

CASE 3.—Mrs. LeF., aged 57 years, had the menopause five years previous to operation. Operation on July 25, 1938 consisted of vaginal hysterectomy for uterine prolapse. The symptoms present prior to operation had consisted of occasional hot

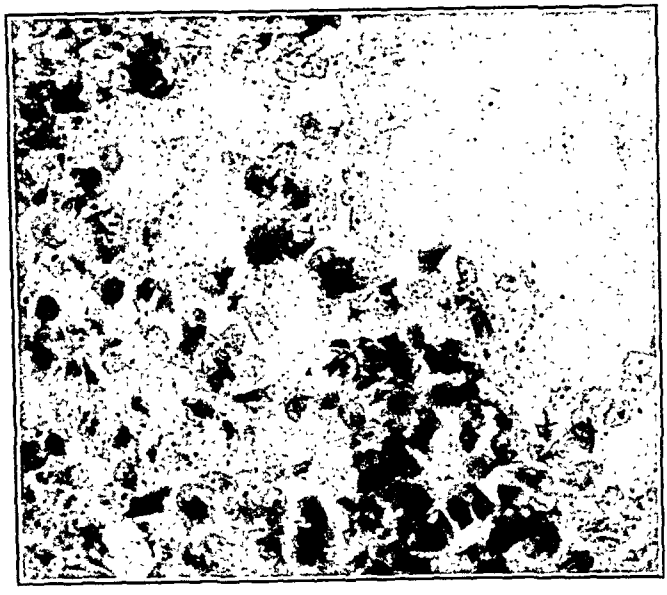


Fig. 3.—After daily increase of parenteral therapy to 3,000 units on the sixth day and institution of oral therapy up to 4,000 units of amniotin. Complete absence of basal cells, only occasional leucocytes and normal cornification.

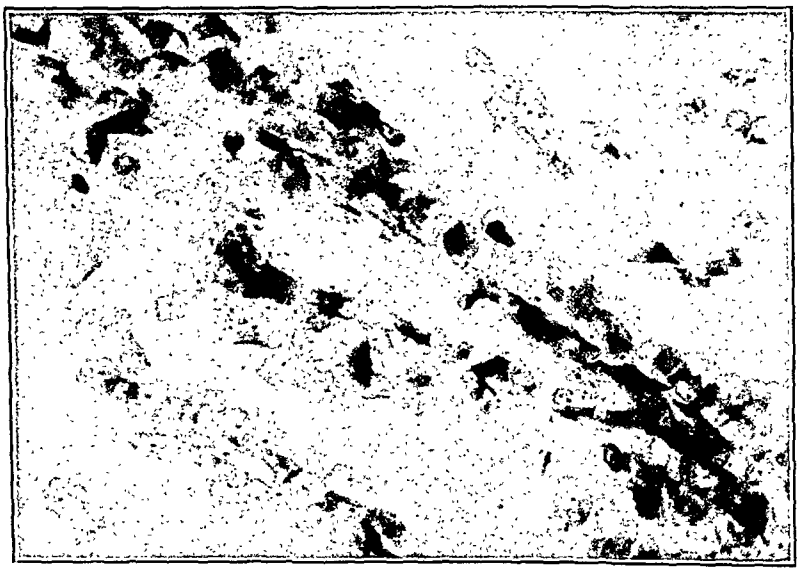


Fig. 4.—Total absence of basal cells and leucocytes and normal cornification as maintained in a case of artificial menopause of long standing by means of oral therapy only and accompanied by complete absence of previous symptoms.

flushes, hypertension, blood pressure 190/94, moderate exhaustion, nervousness, irritability, and insomnia. Recurrence of symptoms early in convalescence was controlled by means of parenteral amniotin in oil, and on July 30, 1938 oral therapy of 50 units of progynon tablets, q.i.d., was found sufficient to maintain relief of symptoms. On August 27 dizziness, nausea and vomiting, and exhaustion occurred which were promptly relieved on cessation of therapy, and medication was reduced

to one tablet, b.i.d. Further reductions were necessary on September 6 to 1 tablet b.i.d. and on September 24 to 1 tablet every second or third day. October 1: Blood pressure 164/90.

CASE 4.—Miss L. A., aged 43 years. Subtotal hysterectomy Oct. 2, 1938 with removal of 440 gm. fibroid uterus. Ovaries normal and not removed. The symptoms prior to operation were nervousness and irritability (weeping and depression), back-

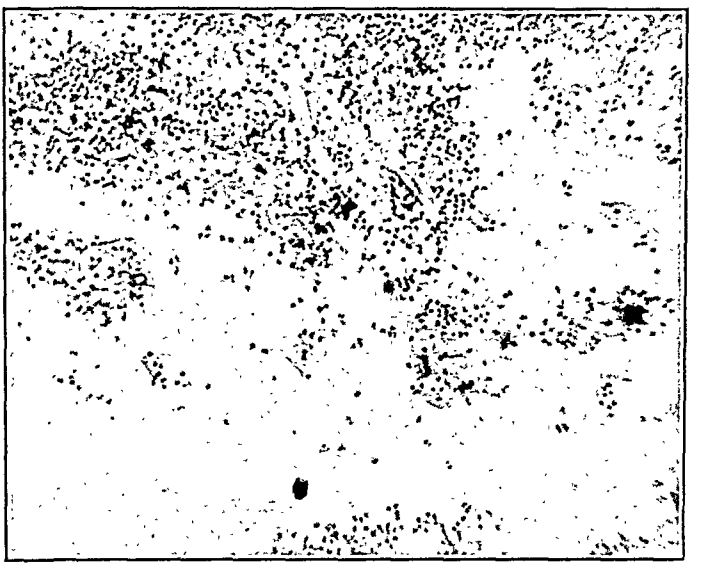


Fig. 5.—(Case 1.) Seven days prior to total hysterectomy. Occasional basal cells, extensive leucocytic infiltration and decreased cornification. Preoperative therapy of 0.5 dram of emmenin, q.i.d., was found adequate.

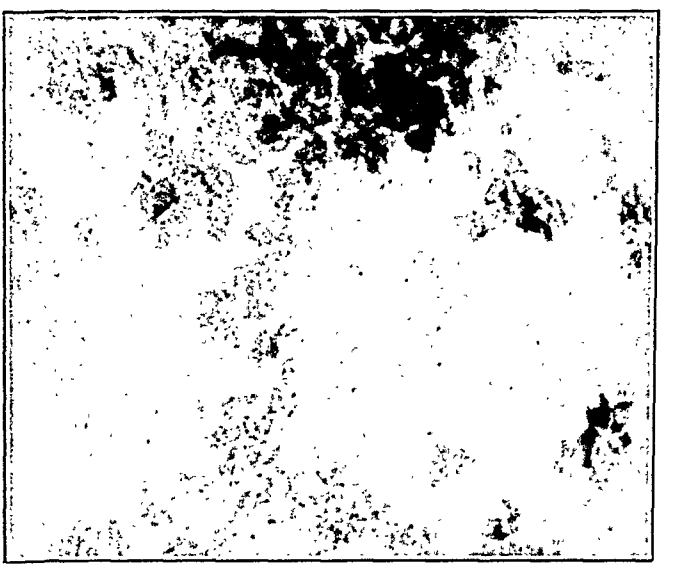


Fig. 6.—Two months after operation with increased postoperative therapy of 1 dram of emmenin, t.i.d. Occasional leucocytes and decreased cornification indicating increased therapeutic requirements.

ache, leg-ache, and headache five to seven days prodromal to the menses. These symptoms were accompanied by a menorrhagia. Excessive menstrual flow of ten to twelve days' duration. On the fifth postoperative day the above symptoms recurred with the exhaustion and backache greatly exaggerated, accompanied by nausea and vomiting. Immediate temporary relief followed administration of 500 units of

amniotin parenterally and was maintained by oral administration of 1 dram of emmenin, q.i.d. By Feb. 3, 1938 symptoms had increased in spite of constant maintenance of original oral medication with the additional occurrence of hot flushes. Fifty units of progynon tablets, q.i.d., were necessary to obtain complete symptomatic relief. Reduction of dosage to 1 tablet daily was accomplished and by February 17 the medication was reduced to 1 dram of emmenin, q.i.d. Therapeutic requirements were further reduced by August 1 to 0.5 dram of emmenin, b.i.d., and since September 17, patient has been symptom-free on 0.5 drams daily.

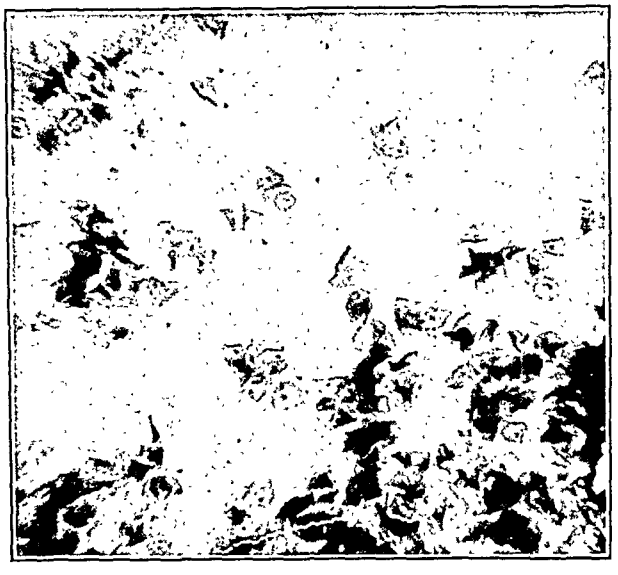


Fig. 7.—One month after therapy had been increased to 1 dram of emmenin, q.i.d. Absence of basal cells, normal cornification and only occasional leucocytes.

SUMMARY

Conclusions and observations derived from the combined study of 519 cases may be summarized as follows:

Any combination of symptoms of the syndrome occurring prior to, during or after the so-called "menopause" must be given consideration as evidence of estrogenic deficiency.

Clinical response provides an accurate and delicate criterion for confirmation of diagnosis and determination of therapeutic requirements whenever these symptoms are encountered.

Therapeutic results may be more promptly and effectively obtained by accurate determination of therapeutic requirements which vary in each instance.

Early institution of therapy results in more prompt and effective response with smaller dosages than late or delayed therapy.

While parenteral therapy is most effective for the determination of therapeutic requirements, oral therapy provides a more satisfactory and sustained effect.

Vaginal smears provide an efficient and accurate index to physiologic action of the estrogens and although of value in the individual case are not essential routinely.

Prophylactic estrogenic therapy in artificially induced menopause is suggested. Although the method has been utilized in only 21 cases

of artificially induced menopause the significance of the results would seem to be considerably enhanced by the rather similar results of the entire series of 519 cases.

I desire to express my appreciation to Dr. Tom Paul for his assistance in obtaining photomicrographs, and to Ayerst, McKenna and Harrison, and E. R. Squibb and Sons for estrogenic substances provided.

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DISCUSSION

DR. J. J. SWENDSON, St. Paul, Minn.—While not ignoring the value of laboratory controls such as vaginal smears, Dr. Schneider has emphasized careful clinical observations, and his results indicate that the relief of more remote symptoms than those commonly attributed to the menopause can be obtained by estrin therapy alone.

While there may be some difference of opinion as to how frequently the more remote symptoms Dr. Schneider has enumerated are directly due to estrin deficiency, his observations and results indicate that we would profit by looking for them oftener and relating them oftener to the menopause.

DR. JEAN PAUL PRATT, Detroit, Mich.—It is very commendable that Dr. Schneider has undertaken to study the vaginal smears to observe the response to estrogenic therapy. This gives a concrete measure of therapy. When one limits oneself to the field of subjective symptoms, there is an opportunity for speculation. Until we have developed some measure of emotion and emotional changes, I believe it is going to be very difficult to establish a rational, specific therapy.

There is one thing to be borne in mind in interpreting vaginal smears. We know estrogenic hormone is selective in its action in the reproductive tract and that the vaginal tissues are those most affected. As we go higher in the genital tract and to other parts of the body, the effect is less conspicuous.

DR. SCHNEIDER (closing).—In my experience with the administration of the estrogens and progesterone I have seen no evidence that permanent damage has ever been done. This I believe is due primarily to the fact that in dealing with estrin and progesterone we are dealing with pure and standardized chemical substances, the effect of which is very transitory. Excessive therapy is always followed by adverse symptoms of such severity that if not ordered to do so the patient will voluntarily discontinue treatment with complete disappearance of adverse symptoms within a few hours.

It is in the utilization of the various pituitary factors that conservatism is most indicated. The fact that the various pituitary factors are available in standardized preparations has caused us to lose sight of the fact that these preparations are not chemically pure. Clinical results with the use of pituitary have failed to produce constant results and in some instances distinctly harmful results have been observed. It therefore seems advisable that pituitary therapy should be used very cautiously and that possibly its utilization should be limited to investigative work until such a time as every factor becomes available in pure chemical form.

THE DULUTH OBSTETRIC RECORD*

RUSSELL J. MOE, M.D., DULUTH, MINN.

IT IS generally agreed that the obstetric records of many private hospitals are inadequate for an accurate factual survey of the obstetric procedures carried out and the results obtained. The chief reason for this is the fact that too often the record is completed weeks or even months after the patient is discharged from the hospital and the details are at best very vague. Another responsible factor is that the data are recorded by all the physicians who happen to be practicing obstetrics in a given hospital, and their knowledge of various procedures, their appreciation of indications and results vary so much as to make many of the records inaccurate. Thus the record loses its value for accurate statistical studies.

While casting about for a method of improving this situation, Dr. J. R. Manley of Duluth established in 1931 a procedure by which all the desired obstetric data were recorded on a large sheet similar to a large ledger sheet, and kept in a separate ledger book. These sheets are printed in such form that they are simple, easily filled in and still contain all the information which is important for future study and analysis. The sheets are bound in a sectional post binder, which permits removal as desired. There are two sheets, one on each side of the ledger, and they are ruled and numbered so that each set of two sheets will record thirty-six cases completely.

There are several cardinal principles to be followed in keeping a record of this sort. In the first place, someone must be responsible for supervising the record. It will not take care of itself even after it is once started. Either the chief of obstetrics or a member of the staff interested in the record should be responsible for supervising the recording of the data. The actual work may be performed by a resident or an interne, but because the latter changes services frequently it is important that he be constantly instructed as to the purpose of the record and the manner in which it is to be filled in, so that all tabulations are uniform. Second, the book should be kept on the maternity floor, where it is readily available and may be filled in from day to day. The third important principle is that the record should be kept up to date. The data are recorded either while the patient is still in the hospital or on the day of discharge, and therein lies its value, for important details are added which would otherwise be forgotten.

The time required to fill in these data is insignificant. Much information is recorded merely by a check mark. Actual timing has demonstrated that it requires approximately two minutes per case. Thus in a hospital having a hundred deliveries a month the time required to record the data would average less than ten minutes a day.

The Duluth obstetric record has given us more accurate and more adequate information regarding the obstetric procedures carried out and the results obtained in our hospitals. The record will readily produce data available for statistical study on problems of interest to the staff and to the hospital. This fact encourages a critical review of certain procedures to the benefit of all concerned. It has been interesting to note that this record unconsciously fosters conservatism in that an obstetrician will be more hesitant to use the radical procedures and manipulations if he knows that the indications and results are to be recorded and critically reviewed.

The record also serves as a practical cross-index system. Certain types of cases may readily be selected for study and analysis. Another important value of the record is that the Chief of the Obstetrical Department may quickly glance over the record for the preceding week or month and know exactly what has happened in his department during that time. This goes hand in hand with what was previously

*Presented at the Annual Meeting of the Central Association of Obstetricians and Gynecologists, Minneapolis, Minn., October 6 to 8, 1938.

Hospital Number	Obstetrician	Para	Age	Prenatal	Wassermann	Pregnancy Toxemia, Bleeding, Etc.	Delivery: Spontaneous	Forceps: Low	Forceps: Mid.	Forceps: High	Breech	Version	Cesarean	Embryotomy	Indication	P. P. Bleeding: Severe	P. P. Bleeding: Uterus Packed	Maternal Injury: 1° Laceration	2° Laceration	3° Laceration	Central Episiotomy	Lateral Episiotomy	Cervix Repaired	Rupture Uterus	Maternal Morbidity: By A. C. S. Standard	Pyelitis	Breast	Inf. Perineum	Other Morbidity	
1																														1
2																														2
3																														3

| | Labor Induced: Toxemia | Post-Maturity | Convenience | Emergency | Method: Castor Oil | Quinine | Pituitrin | Bag | Bougie | Packed | Rupture Membranes | Eclampsia: A. P. | Eclampsia: P. P. | No. of Fits | Placenta Previa: Marginal | Partial | Central | Treatment: Rupt. Membrane | Packing | Bag | Version | Section | Abruptio Placentae, Treatment: Conservative | Section | Maternal Mortality: Cause | Remarks | Baby: Wght. Grm's | Premature | Still Born: Cranial Injury | Paralysis | Fracture | Dystocia | Macerated | Born Alive: Injury | Atelectasis | Premature | Bleeder | Asphyxia | Monster | Born Alive but Died in Hospital: Remarks | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
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Chart 1.—The Duluth obstetric record, showing headings on front and back of each ledger page. There is provided space for 36 individual case records.

stated about the record fostering conservatism. Finally, when the information is recorded by an interne or resident there is a greater possibility of obtaining an unprejudiced report than when the data are recorded by the doctor responsible for the case.

The record has been changed in minor details from time to time to facilitate tabulation and to improve its value. Some hospitals may wish to change the manner of tabulation or the type of material to be tabulated. It is not a perfect record, but one which will add much to the obstetric department of any hospital if properly compiled and critically reviewed for the benefit of the staff.

A REPORT OF THE COMMITTEE ON THE INDUCTION OF LABOR

This report is based on a questionnaire circulated among the members of the Central Association by the Committee on Clinical Affairs during the year 1938.

One hundred and sixty-two physicians (60 per cent) of a total membership of 276 in this Society replied. This is less than the 74 per cent of responses to the questionnaires sent out in 1936. Of the 162 questionnaires that were returned, 125 (45 per cent of the total membership) were answered in sufficient detail to form a basis for study. The remaining 37 questionnaires yielded the following information: 22 were returned without comment, 7 members had not practiced obstetrics during the period of time covered by the questionnaire, 3 had been ill, one was not in practice, and 3 refused to answer the questionnaire and stated that this type of investigation was of no value.

The report of the committee is therefore based on an analysis of 125 anonymous replies to a questionnaire. This group of physicians delivered 13,891 women, almost 2,000 more than were delivered by 132 physicians in 1935. An attempt was made to induce labor on 1,669 (12.2 per cent) of these 13,891 patients and was successful in 1,525 (11 per cent) after the first, second, or third attempt. Thus, 91 per cent of inductions of labor were successful.

Early in the tabulation it became apparent that a comparatively small number of physicians employed induction of labor much more frequently than did the remainder of the group. Because of this fact those physicians who had delivered more than 15 per cent of their patients after labor was induced were designated as Group A. Twenty-six (20 per cent) of the physicians answering the questionnaire are in this group. They delivered 3,477 (23 per cent) of the total of 13,891 patients. Induction of labor was performed by them in 838 (24.1 per cent) of all the patients delivered by them in 1937. Therefore, these 26 men are credited with 55 per cent of the successful inductions of labor. The remaining 99 physicians are designated as Group B. They induced labor on 687 (6.6 per cent) of these 10,314 patients.

Labor was induced on 372 patients because of maturity, on 321 because of postmaturity, on 313 because of toxemia, on 289 for the convenience of the patient, on 56 for the convenience of the obstetrician, and on 82 because there was a large baby. Sixty-five patients had small pelves, 18 had placenta previa, 10 had premature separation of the placenta, 11 had heart disease and 6 were tuberculous. Eighty-nine (5.1 per cent) of the inductions were not explained or were for miscellaneous reasons.

The physicians in Group A performed 212 (73 per cent) of the total of 289 inductions for the convenience of the patient. Group B physicians designated toxemia of pregnancy as the reason for induction more than twice as frequently as did those in Group A.

Toxemia was the reason for induction more frequently in primiparas than in multiparas. Induction was successful in the vast majority of pregnancies associated with toxemia during or after the thirty-sixth week. Some effacement and dilatation of the cervix was usually present in these patients. A combination of drugs and measures recognized as oxcytocics plus rupture of the amniotic sac were used to terminate pregnancy in over 60 per cent of toxemic patients.

The number of successful inductions of labor increased with the duration of pregnancy. Thus, 265 successful attempts were made from the twenty-eighth to thirty-fifth week, inclusively; 603 from the thirty-sixth to thirty-ninth week, and 801 during the fortieth week of pregnancy and thereafter.

The influence of effacement and dilatation of the cervix and the nature and engagement of presenting part were studied in primiparas and multiparas who had experienced successful induction of labor. It was found that 461 primiparas and 406 multiparas had cervices that were effaced and partially dilated compared to 173 primiparas and 148 multiparas who had uneffaced cervices. Therefore, the patient in whom the cervix is effaced and partially dilated has almost three times the chance of successful induction compared to the patient in whom the cervix is not effaced. Induction was successful in 34 patients with breech presentations but 11 others with uneffaced cervices in whom breech presentation occurred failed to respond to artificial stimulation. Labor ensued following stimulation when the vertex was engaged in 455 primiparas and 254 multiparas while 102 primiparas and 200 multiparas failed to go into labor with an unengaged presenting part. Therefore, the primipara who has a cervix that is effaced and that has begun to dilate, and in whom a vertex presentation is engaged, has at least a 75 per cent better chance of going into labor following induction than if the above requirements are not present. On the other hand, multipara responded to induction of labor whether the presenting part was engaged or not, provided the cervix was partially dilated.

Prolapse of the umbilical cord occurred in 30 of the 13,891 patients. Spontaneous labor was complicated by 22 (0.17 per cent), prolapses and induced labor by 8 (0.52 per cent). This complication occurred four times (0.15 per cent) in spontaneous and four times (0.47 per cent) in induced labors cared for by Group A. In Group B there was an incidence of 18 (0.18 per cent) prolapses in 9,650 spontaneous and 4 (0.58 per cent) prolapses in 687 induced labors. Prolapse of the cord occurs three times more frequently with induced labor. The incidence is not influenced by the individual physicians, for it occurred as frequently with those performing a high percentage of inductions as well as those doing them occasionally.

Twenty of the 125 physicians considered that the first stage of labor was lengthened after induction of labor. However, only two of the 26 physicians in Group A who induced labor frequently reported that they believed the second stage to be longer than normal. The majority were of the opinion that it shortened labor.

Quinine for the induction of labor was used by 66 (58 per cent) of the 113 physicians answering this portion of the questionnaire. The majority of those who prescribed this drug appreciated its shortcomings and dangers for the usual total dose varied between 10 and 15 gr. Twenty to 60 gr. in divided doses over a period of twenty-four hours was advocated by two physicians.

Pituitary extract or one of its fractions was used by 83 (75 per cent). The group practicing induction most frequently administered it most commonly. Only 4 preferred not to use it. One to two minims hypodermatically for a total of 5 to 10 minims every one-half to two hours were injected. As much as 4 minims every one-half hour for 8 doses was the maximum amount advocated. Five physicians preferred nasal applications and used 1 c.c. of the extract on an applicator.

Rupture of the amniotic sac was also the method of choice for these 83 members. Group A physicians employed it most extensively for only two reported adversely.

Bags, and especially bougies, were not popular. Practically all physicians employing one of these two methods prefaced their answers by limiting their use to very definite complications. Thirty-two (35 per cent) believed in bags and 11 (9.6 per cent) in bougies.

In order to determine what method or combination of methods was most effective in the induction of labor all cases were placed in five classifications made up as follows: (1) Castor oil, quinine, strychnine and enema, separately or in combination; (2) any or all of the ingredients used in "1" plus pituitary extract; (3) any or all of the ingredients used in either "1" or "2" or both plus rupture of the amniotic sac; (4) any or all of the ingredients used in "1" or "2" plus the introduction of a bag; (5) the same as "4" except a bougie instead of a bag.

Method 1. 407 (70 per cent) of the patients went into labor.
Method 2. 205 (80 per cent) of the patients went into labor.
Method 3. 649 (97.5 per cent) of the patients went into labor.
Method 4. 42 (93 per cent) of the patients went into labor.
Method 5. 12 (86 per cent) of the patients went into labor.

The success of the method did not differ whether used in primiparas or in multiparas. Rupture of the amniotic sac alone or in combination with any part of Classifications 1 and 2 resulted in the highest percentage of successful inductions. Group A physicians used this method 427 times with only two failures. Group B used it only one-half as often.

Of the 13,891 pregnant women attended by the 125 obstetricians, 12 (0.08 per cent) died. Labor was induced in 7 of these but none of these deaths were directly attributable to the induction of labor. In Group A there were two deaths; one the result of a severe nephritic toxemia followed by anuria during the seventh month of pregnancy. The other death resulted from cardiac failure during the last month of pregnancy. In Group B 5 fatalities were reported. (1) Sensitiveness to the drugs nembutal, paraldehyde, and benzyl alcohol; (2) ruptured left ovarian abscess; (3) a patient with pre-eclampsia in whom labor was induced by rupture of membranes and injection of pitocin, followed by post-partum eclamptic convulsion, coma and death seven hours following delivery; (4) a patient in whom cerebral hemorrhage occurred without toxemia. Labor was induced by rupture of membranes but the patient remained undelivered eight hours following admission; (5) a case of post-partum hemorrhage occurring one hour after labor. This was preceded by uterine inertia, unengaged vertex, castor oil, quinine, pituitrin, bag induction, manual dilatation of cervix, internal version and extraction, repair of cervix and perineum under spinal anesthesia.

The elevation of temperature above 100.5° F. for two or more consecutive days following induction of labor was reported to occur no more frequently in induced labor by 115 of those responding to this inquiry. However, 10 were of the opinion that hyperpyrexia and lacerations were more common. One of the cervical lacerations occurred following the expulsion of a Voorhees' bag.

The uncorrected fetal mortality rate for the 13,891 deliveries was 1.6 per cent. There were 150 (1.2 per cent) fetal deaths in the patients who had no induction of labor and 78 (5.1 per cent) in those who experienced labor after some method of induction. The highest rate occurred in Group B where 99 physicians induced 687 labors. Of these 687 pregnancies, 52 (7.5 per cent) resulted in stillbirths. In Group A the stillbirth rate was 3.1 per cent less than one-half of that mentioned for Group B. It appears that this lower rate for Group A was due to the frequent use of rupture of membranes for induction of labor where the indication for the procedure was maturity, postmaturity, or convenience of the patient.

Prematurity was given as the cause of fetal death in 23 of the 78 fetal deaths that occurred after labor had been induced and prematurity with toxemia for an additional 10 more. Death in utero before onset of labor accounted for another 10 infants. There were 9 deaths from congenital defects such as monsters, atelectasis and cardiac failure. Three were lost because of placenta previa and premature separation of the normally implanted placenta. This leaves 23 (30 per cent) of the deaths of infants born following induction of labor to be explained. Five died of cerebral hemorrhage, 5 from dystocia, another 5 from prolapsed or knotted cord, 3 from asphyxia, and the cause of 5 deaths was undetermined. Accepting labor as the cause of death in this group in whom labor was induced the fetal mortality may be corrected from 5.1 per cent to 1.5 per cent.

In order to ascertain the influence induction of labor might have on cesarean section, the problem was studied from the standpoint of type of induction, time interval between attempted induction and operation, type of cesarean section performed, subsequent complications, and the outcome as to whether the patient lived or died.

There were 19 cesarean sections performed after labor had been induced. Twelve were classified as low, six as classical, and one as a Porro cesarean. Three low and two classical sections were done six to thirty-six hours following 4 medical inductions

combined with artificial rupture of the membranes and one insertion of a bougie. The other 14 patients experienced medical induction prior to their operation. The indication for the Porro operation was given as "disproportion proved by x-ray." The 5 sections performed by Group A physicians were done following attempted medical induction. Only 5 of the 19 cesarean sections were done by Group A. No complications or deaths were reported.

All except 14 physicians answering questionnaires commented upon the use of induction of labor. One hundred considered some combination of medicines and rupture of the amniotic sac a safe and valuable procedure. Rupture of the membranes in primiparas in whom pregnancy had approached or passed the date of expected confinement, in whom the presenting part was engaged, the cervix effaced and partially dilated and in multiparas in whom the pregnancy was at term and the cervix partially dilated, in general was considered the safest, most rapid, and satisfactory method of induction of labor.

There were some physicians who routinely prescribed "castor oil and quinine for all patients when they were at term." Others were fearful of quinine because of the tetanic effect on the uterus and toxic influence of the fetus. Pituitary extract given in small doses by hypodermic injection or by intranasal application were advocated by some but many condemned larger doses.

There were 5 individuals who considered all methods except castor oil and enemas meddlesome and dangerous. One thought that none of the methods was worthy of trial, two considered bags, and one considered bougies the best offensive weapon. One now prefers cesarean section instead of induction when pregnancy is complicated by toxemia or heart disease. Walking to the point of fatigue was advocated for the reason that it assisted in effacing and dilating the cervix. If this failed medical induction was used, if necessary followed by rupture of the membranes.

Bags and bougies were generally condemned with the exception of the few cases mentioned. One had an "abhorrence and fear of bags." Infection, cervical lacerations, hemorrhages, and the necessity for version and extraction were said frequently to follow their introduction. One member considered "induction as a necessary evil of obstetric practice."

The Committee desires to express its appreciation to those individual members of the organization who, by giving of their time to fill out the questionnaires, have made possible this statistical report of induction of labor for the year, 1938.

The task has been a pleasant and a profitable one, and it is hoped the results will prove as interesting to the membership at large as they did to the Committee.

R. S. Cron
L. M. Randall
N. R. Kretzschmar

DISCUSSION

DR. LAWRENCE M. RANDALL, Rochester, Minn.—I do not propose to interpret for you the statistical data in this paper; I think that is a thing for each individual member of the Society to evaluate himself, depending upon his attitude concerning the induction of labor. I would like to make this comment about the induction of labor in general.

It is difficult to conceive that one could practice obstetrics without some method of terminating pregnancy in patients who have toxemia of the latter months of pregnancy or in whom placenta previa occurs. Such instances as a patient with a contracted pelvis or one who has a diseased heart in whom it is desirable to shorten the length of pregnancy are not infrequently encountered. In addition there are a large number of women apparently at term in whom the vertex is engaged, the cervix completely effaced and partially dilated but in whom labor does not occur spontaneously.

We have considered the inductions of labor that are necessary or urgent; inductions that are employed from a prophylactic or preventive standpoint; and, last, inductions that may be considered optional.

An induction of labor that is necessary because of danger to the lives of the mother and the fetus if pregnancy continues may allowably be more drastic than one

that is optional. In the latter instance a medical induction may be attempted, such as castor oil followed by small doses of extract of pituitary given every half hour until labor is initiated or until ten such doses have been given. If this fails in the optional cases I seriously doubt that further interference is justifiable. The failure may be excellent evidence that the pregnancy is not yet at term. On the other hand, given a patient with a toxemia in whom induction of labor is necessary the addition of rupture of the amniotic sac is thoroughly justifiable. It seems to me that care should be used in selecting that method of induction best suited for the individual case in order that the subsequent conduct of labor is not compromised.

The statistical data contained in this report will naturally be variously interpreted according to the individual conceptions of the members of this Society toward methods of induction of labor.

In closing, I should like to emphasize that 13,891 women were delivered by 125 members of this Society with a loss of only twelve patients, a maternal death rate of 0.08 per cent; in addition, there was an uncorrected fetal mortality of 1.6 per cent. It seems to me that the members of this Association may well be proud of such a low maternal and fetal mortality.

(The paper of Drs. P. B. Russell, Jr. and M. J. Roach will appear in the June issue of the JOURNAL.)

ITEM

Central Association of Obstetricians and Gynecologists

The Eleventh Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held at Kansas City, Mo., November 2, 3, and 4, 1939. For further information apply to Dr. William F. Mengert, University Hospital, Iowa City, Iowa.

DYSGERMINOMA

With a Report of Nine Cases, One Associated With Pregnancy

Malcolm B. Dockerty, M.D., and
William Carpenter MacCarty, M.D., Rochester, Minn.
(From the Department of Pathology, the Mayo Foundation, and the Section on Surgical Pathology, the Mayo Clinic)

THE existence of a type of solid ovarian neoplasm with the histologic features of undoubted malignancy and the clinical history of a more benign lesion, has long been recognized. That these neoplasms occurred in young individuals, that they were frequently bilateral and that they were often associated with genital hypoplasia were early observations of prime importance. The close resemblance of their cellular structure to that of the fetal gonad before the stage of sexual differentiation was the observation of Robert Meyer who proposed the name "dysgerminoma" for this neutral type of tumor. The literature on this interesting neoplasm consists in the reports of approximately 200 examples described under a range of terminology varying from "seminoma ovarii" (Chevassau) to "embryonal carcinoma"—a variety which indicates the early haziness surrounding their identification.

CLINICAL FEATURES

Ovarian dysgerminoma has its "male" counterpart in the seminoma testis but runs a much less malignant course than the latter. In addition, there are certain age differences, dysgerminoma occurring usually before the age of twenty years, seminoma after the age of twenty. Among pseudohermaphrodites of both sexes the tumor is of relatively high incidence. The tumor produces no hormones and hence no characteristic menstrual or other secondary sexual disturbances. However, the syndrome of pseudohermaphroditism or of poorly developed genitalia, in a young woman who presents herself with a pelvic tumor, should make one think of the possibility of dysgerminoma.

PATHOLOGY

Dysgerminoma occurs bilaterally in about 35 per cent of cases. Two gross and two microscopic features characterize this solid ovarian neoplasm as an entity. Grossly the neoplasms are nearly all of a peculiar brain-like consistency with broad zones of necrosis and hemorrhage. Microscopically the stromal reaction with lymphocytes and foreign body giant cells is almost pathognomonic. The tumor cells themselves are large and round, with hyperchromatic nuclei, large nucleoli and many mitotic figures. A complete lack of differentiation is outstanding and the grade of malignancy apparently is always 4. The latter finding

probably accounts for the observation of Schiller and others that the tumors are extremely radiosensitive.

MATERIAL FOR STUDY

In an analysis of some 300 solid and solid-cystic tumors removed surgically at the Mayo Clinic from 1921 to 1936, nine examples of dysgerminoma were encountered. The clinical and pathologic features of these cases are reported in some detail.

REPORT OF CASES

CASE 1.—A married white nullipara, aged 29 years, was admitted to the clinic Feb. 7, 1936. She complained of an abdominal tumor. Her family history and personal history were negative. Menses had begun at the age of fifteen years and had

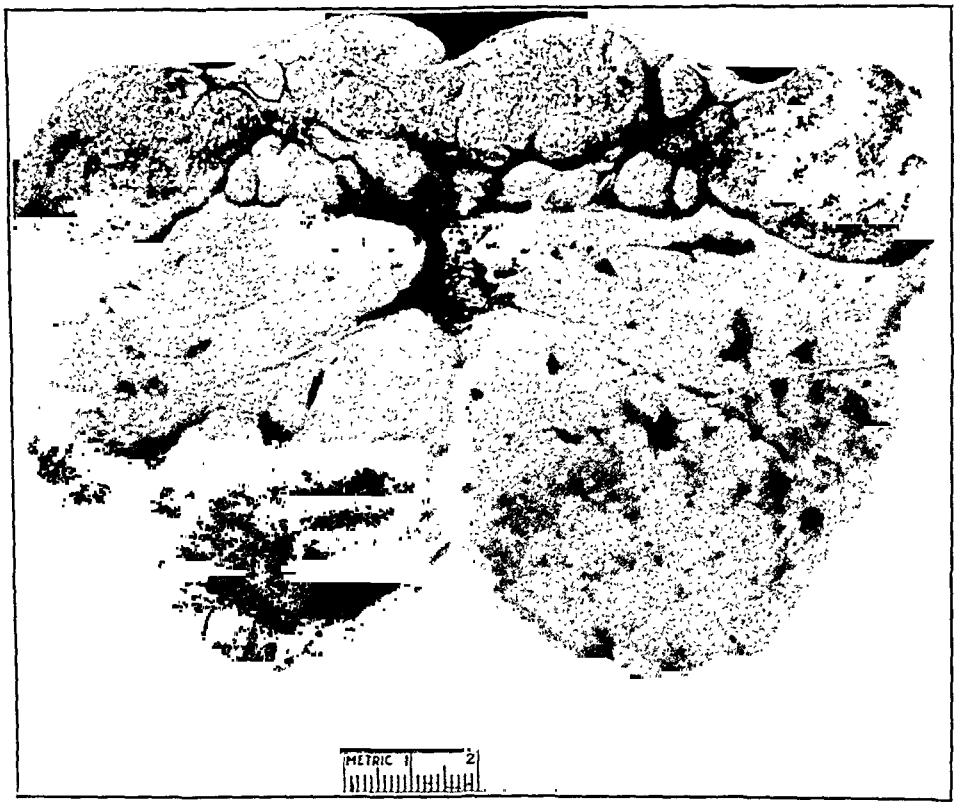


Fig. 1.—(Case 1.) A large ovarian dysgerminoma associated with pregnancy. Note dark regions of hemorrhage and necrosis.

always been scanty and somewhat irregular. Her last period had ended two months prior to registration. One month prior to admission she began to have morning sickness, increasing in severity. She consulted her physician who made a diagnosis of pregnancy associated with an ovarian tumor and advised operation.

Examination revealed a pregnant uterus of a size compatible with the period of amenorrhea. A large adnexal mass was palpable in the region of the right ovary. The results of laboratory tests were essentially negative.

At operation on Feb. 12, 1936, a large, solid right ovarian tumor was removed. Adhesions or metastasis was not noted. She did not receive postoperative roentgen therapy because of her pregnancy which subsequently terminated normally at term. Although she has not returned for re-examination, her present state of apparently good health would indicate that clinical recurrence of the malignant lesion had not occurred.

Grossly the tumor measured 12 by 10 by 10 cm. and weighed 422 gm. It was grayish brown in color, encapsulated, somewhat lobulated and was soft in consistency. On section the tumor was solid throughout. It presented a homogeneously grayish brown appearance, except for some dark zones of hemorrhage and necrosis. The consistency was almost brainlike, being somewhat firmer than that in texture. No trace of normal ovarian tissue could be found on careful searching. Microscopic examination of frozen sections stained with hematoxylin and eosin showed that the tumor was composed of round cells with vacuolated cytoplasm and large dark-staining nuclei containing large nucleoli. Many mitotic figures were present. An alveolar or pseudoalveolar arrangement was occasionally observed but the characteristic cellular grouping was one which completely lacked differentiation. The stroma was loose and very richly infiltrated with lymphocytes. Here and there in the stroma

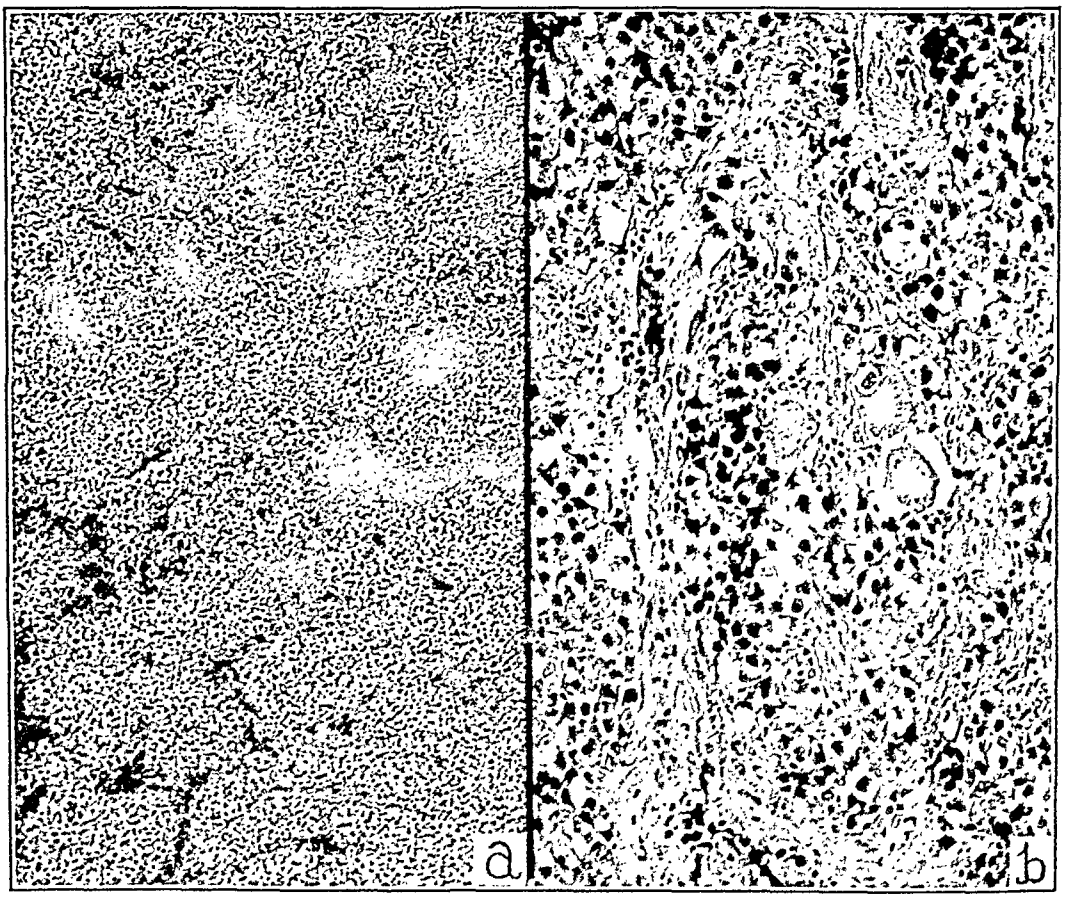


Fig. 2.—(Case 1.) *a*, Ovarian dysgerminoma showing the undifferentiated character of the cells, hemorrhage and degeneration (×45); *b*, ovarian dysgerminoma showing foreign body giant cells in the loose stroma (×200).

were scattered nests of large giant cells of the type associated with foreign bodies. Hemorrhage and necrosis were frequently encountered. In paraffin sections, the cells were seen to have an irregular, shrunken appearance. In preparations stained with sudan III a lipoid substance was demonstrated within the cytoplasm of the giant cells (Figs. 1, 2*a* and *b*).

CASE 2.—A single white woman, aged 19 years, registered at the clinic Sept. 7, 1929, complaining of pelvic pain and irregular menses. Her family history and personal history were negative. Menses had begun at the age of fifteen years and were characterized by scanty flow at long but irregular intervals. Pelvic pain of a dragging character had been present for six weeks prior to consultation.

Examination disclosed a small uterus and a pedunculated, freely movable tumor in the region of the left adnexa. The results of laboratory examinations were negative.

On September 8, 1929, a subtotal abdominal hysterectomy was performed with removal of both adnexa. Postoperatively she had an uneventful convalescence and returned to her home on the eighteenth day without receiving roentgen therapy. She was living and well in September, 1933.

Grossly the uterus was hypoplastic, measuring only 3 by 2 by 2 cm. Both tubes showed mild chronic inflammatory thickening. The left ovary was replaced by a grayish yellow tumor measuring 15 by 11 by 9 cm. in its greatest dimensions. The surface was smooth. On section, the tumor, like that in Case 1, had a homogeneous grayish brown surface with darker regions of necrosis and hemorrhage, resulting in the formation of pseudocysts. Its consistency was soft.

Microscopically the tumor had all of the cardinal features necessary for a diagnosis of dysgerminoma, namely, the presence of large dark-staining malignant cells diffusely arranged in a loose stroma infiltrated with lymphocytes and giant cells of the type associated with foreign bodies.

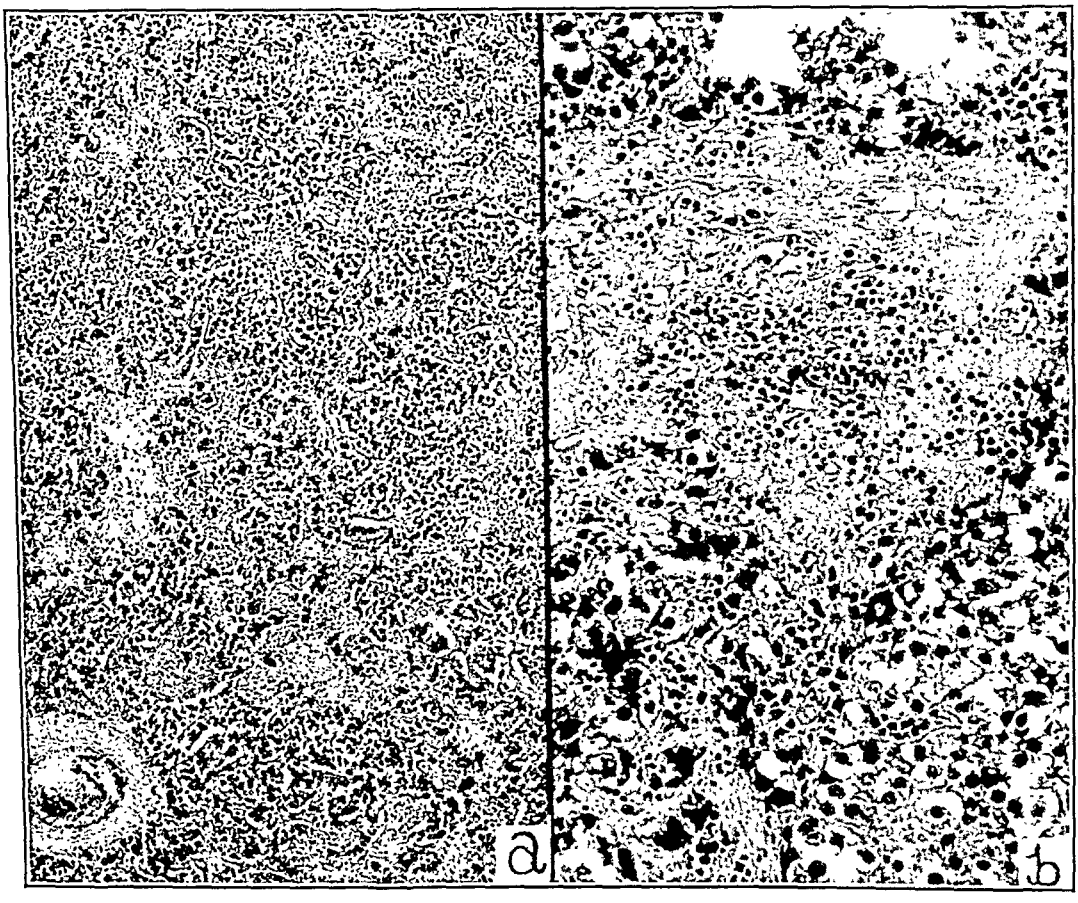


Fig. 3.—(Case 3.) *a*, Typical dysgerminoma. Note loose arrangement of cells with zones of necrosis (×45); *b*, ovarian dysgerminoma showing lymphocytic reaction in stroma (×180).

Grossly the right ovary appeared normal. Microscopically, however, there was a diffuse hilar growth of undifferentiated cells of a character similar to those seen in the tumor of the left ovary.

CASE 3.—A single white woman, aged 18 years, was admitted to the clinic Oct. 29, 1930, complaining of pelvic pain and urinary frequency. Her family history and personal history were negative. Menses had begun at the age of 14 years and had been regular and painless. For ten months she had suffered from pain in her left loin with a distribution suggestive of renal colic. Frequency of micturition and hematuria had been occasionally noted.

Examination revealed a large tumor in the region of her left adnexa. Urinalysis disclosed pus and blood in a specimen obtained by catheterization. Roentgenologic and cystoscopic examinations disclosed a stone in the left renal pelvis.

At operation on Nov. 3, 1930, a large solid cystic tumor was removed. The mass, which appeared to arise from the left ovary, was free of adhesions and metastasis was not noted. The uterus was small.

The patient was advised to return in two months for further observation and treatment of her renal condition. She was not seen again, however, until 1934 at which time the performance of a nephrectomy was necessary because of a functionless left kidney containing a large calculus. At the time of the second operation, evidence of recurrence of the malignancy could not be found.

Grossly the tumor measured 12 cm. in diameter and was similar to those described in connection with Cases 1 and 2. Hemorrhage and necrosis again were prominent features. All traces of ovarian tissue were obliterated. Microscopically the picture was exactly the same as that described in Cases 1 and 2 (Figs. 3*a* and *b*).

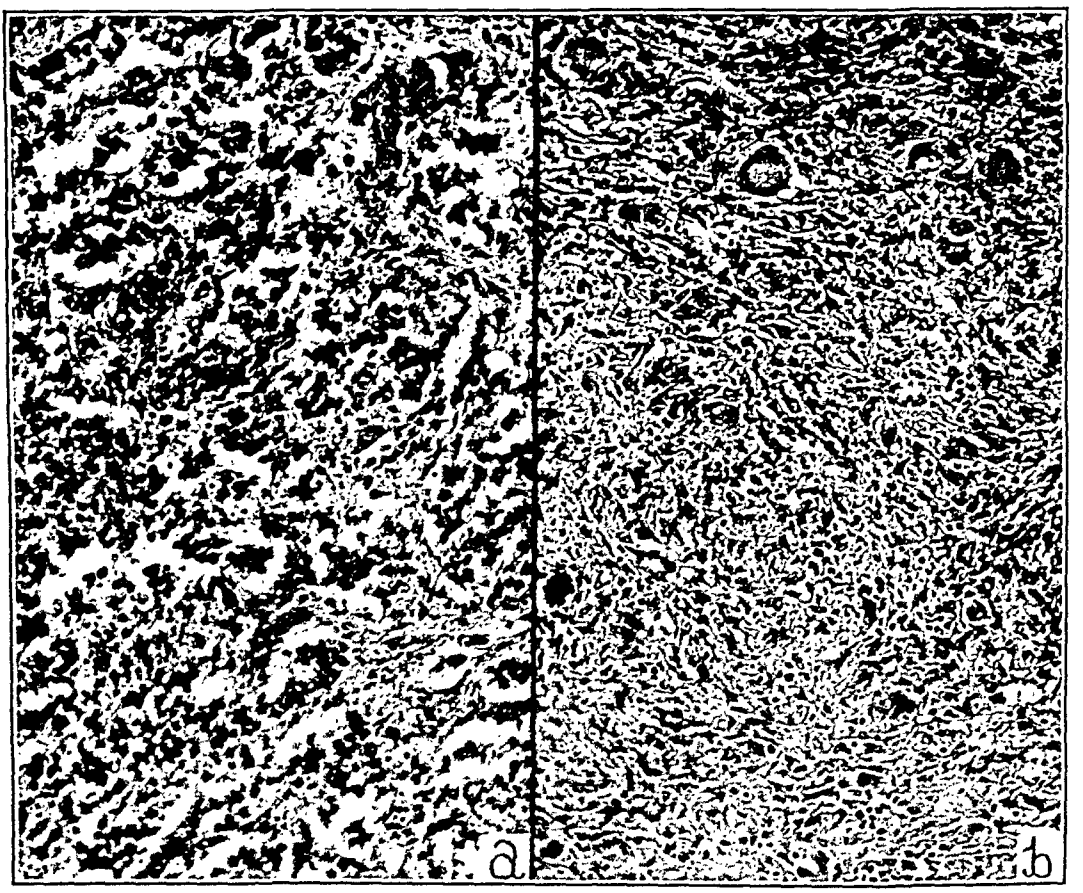


Fig. 4.—(Case 4.) *a*, A typical dysgerminoma (×130); *b*, showing a nest of foreign body giant cells in a zone of necrosis (×100).

CASE 4.—A married white nullipara, aged 29 years, registered at the clinic April 4, 1917, complaining of menorrhagia and metrorrhagia of four months' duration. Two months prior to registration she had noticed a tumor in the lower part of the abdomen. Pelvic examination disclosed the presence of a nodular type of uterus and a mass in the region of the left adnexa.

On April 10, 1917, a Wertheim hysterectomy was performed and both adnexa were removed because of a solid tumor of the left ovary. Several iliac lymph nodes were indurated and were removed. Postoperatively an intensive course of roentgen therapy was administered. This patient was alive and well seventeen years later.

The left ovary was the seat of a solid neoplasm measuring 4 by 3 by 2 cm. The mass was adherent to the uterus which had several small metastatic nodules on its serosal surface. A submucous fibroid also was present. Small iliac nodes measuring 1 to 2 cm. in diameter were manifestly malignant and had, like the primary ovarian

neoplasm, a soft brainlike consistency so characteristic of dysgerminoma. The right ovary grossly appeared normal. Microscopic sections of the ovarian tumor, the uterine nodules and the iliac nodes, all had similar characteristics, namely, those of an embryonal type of carcinoma with hemorrhage, necrosis, lymphocytic infiltration and a foreign body giant cell reaction. The right ovary was free of involvement (Fig. 4, *a* and *b*).

CASE 5.—A single white nullipara, aged 17 years, registered at the clinic July 16, 1928, complaining of scanty menses. Her family history revealed that one sister, aged 11 years, had succumbed following an operation for the removal of a "sarcoma of the ovary." Her personal history was negative. Menses, which had begun at the age of 13 years, occurred at intervals varying from two to four weeks, with scanty flow lasting only one day. Sixteen months previously they had ceased.

Examination disclosed an infantile type of uterus and a hard tumor in the posterior culdesac. At operation July 25, 1928, a solid tumor of the left ovary was

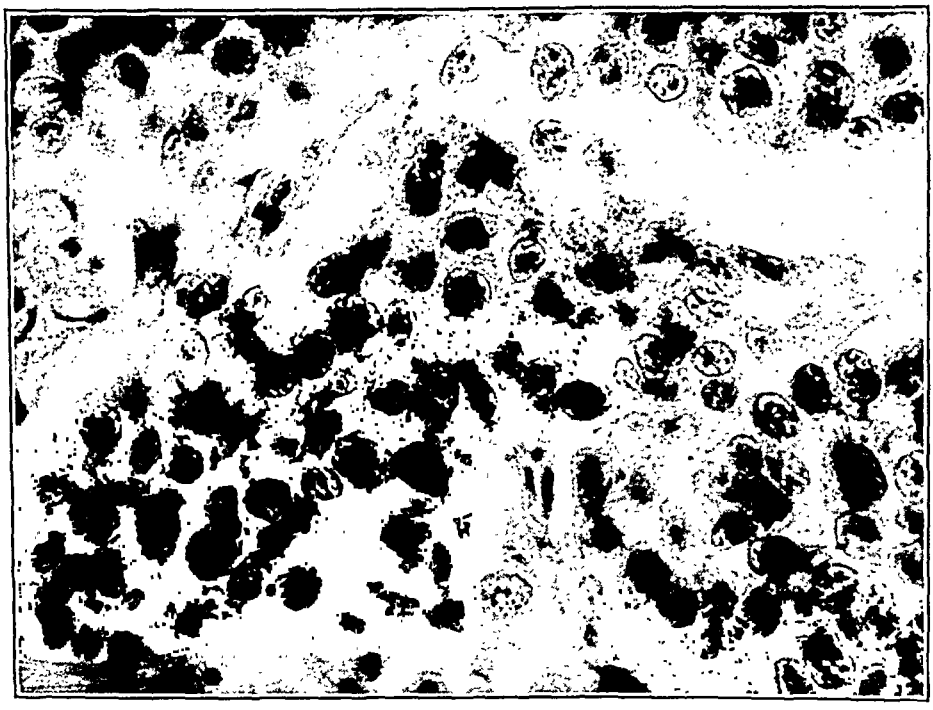


Fig. 5.—(Case 6.) Preparation from a frozen section showing lack of differentiation. Note large nucleoli and mitotic figures (×420).

removed. Adhesions were not noted and evidence of metastasis could not be found. The patient was living six years after operation. Grossly the tumor had the usual features of dysgerminoma. In addition, numerous small deposits of calcium were noted throughout the mass. Microscopically a pseudoalveolar arrangement of the cells was more in evidence than in the previous 4 cases.

CASE 6.—A married white primipara, aged 24 years, registered at the clinic May 28, 1928, complaining of urinary frequency and discomfort of four months' duration in the lower part of the abdomen. The menses had been regular. She had given birth to one child and had experienced one miscarriage. Examination disclosed a firm tumor in the lower part of the abdomen. Its size was commensurate with that of a uterus after four months of gestation. Laboratory data were negative.

On May 29, 1928, a subtotal abdominal hysterectomy was performed with removal of both adnexa because of a solid tumor involving the left ovary. The patient was living and well seven years after operation. Grossly the tumor measured 9 by 8 by 7 cm. and had the features of dysgerminoma. Microscopic sections confirmed the diagnosis (Fig. 5).

CASE 7.—A girl, aged 12 years, was admitted to the clinic Oct. 28, 1927, complaining of enlargement of the abdomen of two years' duration. Seven days prior to registration she began to suffer from pain in the lower part of the back. A local physician called in consultation discovered a tumor of the pelvic cavity. Examination at the clinic confirmed these findings.

On Nov. 5, 1927, a total abdominal hysterectomy was performed with removal of both adnexa because of the presence of bilateral solid ovarian tumors. Both tumors appeared pedunculated. On the right side the mass was freely movable but on the left side there were many adhesions so that complete removal was performed with great difficulty. The patient received a postoperative course of roentgen therapy and was discharged on the eighteenth day following operation. She died at home three months later following the occurrence of symptoms of intestinal obstruction, probably owing to recurrent malignancy.

Grossly the tumors were solid throughout and soft in consistency. The uterus was infantile in type. Microscopic sections of both neoplasms revealed a picture typical of dysgerminoma.

CASE 8.—A single white girl, aged 18 years, was first seen at the clinic on Feb. 8, 1927, at which time a thyroidectomy was performed because of a toxic adenoma. The diagnosis of right ovarian tumor was made at that time, and the patient was advised to return in one month for a pelvic operation. She disregarded this advice but returned Jan. 14, 1931, complaining of backache and discomfort in the lower part of the abdomen. Menses had been regular.

On Jan. 15, 1931, a total abdominal hysterectomy was performed with removal of the adnexa because of a solid tumor of the left ovary. Postoperatively the course was stormy, bronchopneumonia developed and the patient died on the sixth postoperative day. Permission for necropsy was not granted.

Grossly the left ovarian tumor measured 9 cm. in diameter and was a typical dysgerminoma. The right ovary was fibrotic. The uterus was small and contained multiple fibromyomas. Microscopically, sections of the ovarian neoplasm were typical of dysgerminoma. Involvement of the right ovary or of the uterus had not occurred.

CASE 9.—A girl, aged 15 years, was admitted to the clinic July 5, 1935, complaining of a painful abdominal swelling of two months' duration. Menses had always been scanty and irregular and were associated with dysmenorrhea. Her last menstrual period ended two months prior to admission.

On examination a tumor in the left side of the pelvic cavity was disclosed and an extreme degree of ascites was present. On July 12, 1935, a total hysterectomy and bilateral salpingo-oophorectomy were performed because of a left ovarian neoplasm. Many adhesions were noted. The ascitic fluid was bloody. The patient was given roentgen therapy postoperatively but died at her home two months after operation.

Grossly the tumor measured 12 cm. in its greatest diameter. It had the characteristics of dysgerminoma except for the presence of an unusual degree of necrosis and hemorrhage. The uterus was small in size. The right ovary was normal. Microscopically, the tumor was a typical dysgerminoma. Neither the uterus nor the right ovary was involved by metastasis.

COMMENT

Ovarian dysgerminomas are rare tumors. In 1934, Fauvet was able to collect from the literature only 64 cases. Of these, 27 occurred among pseudohermaphrodites, 2 were found among true hermaphrodites and in the remaining 35 instances the patients were otherwise normal. Considering the rarity of the neoplasm, the age of the patients and the frequent association of imperfect gonads, it is not surprising that pregnancy is a very rare complication of this condition. Stabler and Thompson, in 1937, reported such a case. The child was delivered by cesarean section and the tumor was resected

at the same time. A second pregnancy ensued two years later. Doubrère records a case in which the tumor was removed eight days post partum. Several instances of dysgerminoma among parous women have been cited and Case 6 is an additional example. However, we have been unable to find another case of dysgerminoma in which the tumor was removed in the early months of pregnancy as illustrated in Case 1.

The patients all fell into the younger age groups confirming the observations of Fauvet and others that dysgerminoma is more frequent among patients less than twenty years of age. One patient was twelve years of age, the remaining eight patients were all past the age of puberty. Although none of these patients was considered to be a pseudohermaphrodite, in at least five cases there was anatomic and physiologic evidence suggesting sexual inadequacy. In all of the cases in which the uterus was removed, it was small in size. In one of the cases in which the uterus was not removed the surgeon made a note regarding its infantile character.

Irregularity of menses with scanty flow was a symptom in four cases but had been present from the time of puberty and in every case its presence could be explained on the basis of uterine hypoplasia. The menorrhagia that occurred in Case 4 was probably owing to the presence of a submucous fibroid. In Case 7 menstruation had never occurred.

In 4 instances the tumor was noticed by the patient and in one case the tumor was known to have existed for four years. Ascites was a clinical finding in Case 9. The tumors occurred unilaterally in seven and bilaterally in 2 cases. In 2 cases adhesions were present. In one case bloody ascitic fluid was found. Metastasis to lymph nodes was noted in one instance in which the uterus was also similarly involved.

SUMMARY

Nine cases of ovarian dysgerminoma are presented, one complicating pregnancy. All these tumors were found among young individuals. The tumors occurred unilaterally in seven instances. In 5 cases there was associated uterine hypoplasia. In spite of a histologic picture of undoubted malignancy, recurrence followed in only 2 instances.

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NONCONVULSIVE PREGNANCY TOXEMIAS

Their Relationship to Chronic Vascular and Renal Disease

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IN A previous study of eclampsia,[1] the writers divided the investigated patients into three groups for the purposes of studying both their immediate prognoses and their ultimate fates. The *first* group consisted of patients without histories of acute nephritis in whom the blood pressure and urine were known to have been normal before the eclamptic pregnancy. The *second* group consisted of patients in whom the eclampsia was known to have been superimposed upon hypertensive disease or nephritis. The *third* group was made up of patients about whom there was no reliable medical record prior to the eclamptic pregnancy.

Such grouping of patients is helpful with respect to the immediate prognosis in eclampsia, but it is essential in any attempt to evaluate eclampsia as a cause of subsequently encountered hypertension or nephritis. In brief, it was found that the immediate prognosis of eclampsia is most favorable when it is uncomplicated by pre-existing vascular or renal disease, and least favorable in patients with such pre-existing disease. At follow-up examination, an average of 7.6 years after the eclampsia, the gross incidence of hypertension (systolic blood pressure greater than 150) among all cases was 27.5 per cent. However, in the group of patients who were known to have been normal prior to the eclampsia, the incidence of hypertension was only 10.3 per cent, an incidence slightly below that of hypertension in women of this age group, irrespective of pregnancy. Further, in this latter group, there was no instance of albuminuria or impaired renal function. There was no evidence from this series of patients that simple eclampsia causes a subsequent progressive parenchymatous nephritis. The impression was gained that eclampsia in the previously normal patient rarely initiates the chronic vascular degenerative process which results in subsequent progressive hypertension.

In the study of the immediate and ultimate fates of patients with the so-called "nonconvulsive pregnancy toxemias," it would appear to be equally important to arrange them into groups on the basis of what is or is not known about their vascular and renal systems prior to the pregnancy involved. We have examined 700 women at intervals varying from six months to twenty-one years following such so-called "nonconvulsive toxemic pregnancies" and have studied them in groups based upon what we know or do not know positively about the integrity of their vascular and renal systems prior to the pregnancy concerned.[2]

The groups consist of:

1. Patients without history of acute or subacute nephritis and with essentially normal urine who are known to have had vascular hypertension prior to pregnancy.

2. Patients who are known to have had parenchymatous nephritis (glomerulo- or pyelonephritis) prior to pregnancy.

3. Patients without history of acute or subacute nephritis whose blood pressures and urines were normal prior to and in the first three months of pregnancy. These patients are again subdivided into two groups based upon the severity of the hypertension, albuminuria, edema, and symptoms as follows: (a) Pre-eclamptics, Grade I (mild); (b) pre-eclamptics, Grade II (severe).

4. Patients about whom there were insufficient data concerning the status of the vascular and renal systems before pregnancy to permit of excluding antecedent vascular or renal disease.

I. PATIENTS WITHOUT HISTORY OF ACUTE OR SUBACUTE NEPHRITIS AND WITH ESSENTIALLY NORMAL URINE WHO WERE KNOWN TO HAVE HAD HYPERTENSION PRIOR TO PREGNANCY

There are 122 patients in this group whom we have followed from six months to more than three years following pregnancy. Their blood pressures prior to and in the first trimester of the pregnancy concerned varied from 140 to over 200 mm. Hg systolic and 90 to over 120 mm. Hg diastolic. Patients with aortic insufficiency and a number with mild elevation of systolic pressure associated with hyperthyroidism are not included. Our general policy in the management of these cases is as follows:

When first seen, after history and physical examination with particular emphasis on the heart and vascular system, the response of the blood pressure to a period of rest is observed, the catheter urine is examined, and a renal concentration test is performed. If the heart is not enlarged, the systolic and diastolic blood pressures show considerable decrease with rest to near or within normal limits, the catheter urine is normal, the specific gravity is in excess of 1.020, and the prognosis for pregnancy is regarded as relatively favorable under the strict regime to be subsequently outlined.

Patients with considerable elevation of blood pressure, evidence of structural vascular change in the eye grounds, enlargement of the heart, vascular symptoms such as dyspnea, vertigo, and headache are admitted to the hospital for more complete study. In these cases, the response of the blood pressure to several days of bed rest, the seven-foot heart roentgenogram, the electrocardiogram, and the renal function are further investigated.

After consideration of the age, parity, physical and laboratory findings, decision is made as to whether pregnancy should be continued. In general, any evidence of impaired renal function, cardiac disease or enlargement, structural vascular change as seen in the retinal vessels, or persistence of systolic pressure over 150-160 mm. Hg or over 100 mm. Hg diastolic after bed rest, have been considered sufficient indication for offering therapeutic abortion. If the changes are marked, termination of the pregnancy is urged; if they are borderline, the situation is explained and the patient's wishes are weighed.

Upon this general basis, 17 therapeutic abortions have been performed in this group of 122 patients. Ten of these were abdominal hysterotomies with sterilization, and 7 were pelvic abortions. There were no deaths. Interruption of pregnancy was advised and refused in a number of instances. There was only one patient, under thirty years of age, in the group whose pregnancies were interrupted and only one who did not have either a proved cardiac enlargement, marked retinal vessel sclerosis, or both. None showed evidence of renal insufficiency, although small amounts of albumin were present in the urine of half of them. The urea clearance was 64 per cent in one instance. In all others, it was above 70 per cent. Even one patient who died one year after therapeutic abortion from complications resulting from her vascular disease showed urea clearances of 100 per cent and 168 per cent, respectively, prior to interruption.

In the remaining group of 105 patients in whom pregnancy has been permitted to continue under strict regime, there were only 8 who had cardiac enlargement, 7 of whom delivered full-term living babies. The other patient had stillborn twins of thirty weeks gestational age, following induction of labor because of the fear of impending eclampsia.

None of these 105 patients had any evidence of renal insufficiency clinically or by laboratory findings. However, the initial catheter sediment revealed 4 to 6 white blood cells per high power field in 25 per cent of the cases, and two patients had significant pus in the urine. We are aware of the possibility of unrecognized pyelonephritis as a background for the hypertension, but it would appear difficult to evaluate the significance of the occasional pus cell in an otherwise normal urine sediment of these patients, most of whom were multiparous with varying degrees of cystocele. We have reported the urine sediment in the initial catheter specimens for the reason that pregnant women at bed rest do not tolerate repeated catheterization, and after several repetitions, a moderate number of white blood cells are often present.*

The general policy in the ante-partum care of these patients may be outlined as follows:

1. A well-balanced diet, including about 125 gm. of protein, and high in minerals and vitamins is prescribed. Supplementary iron has been prescribed for all patients with even mild anemia.

2. Rigid weight reduction in obese patients is insisted upon. We have seen no harm to such patients if there is no weight gain during pregnancy, or even ten or more pounds weight loss, provided that liberal protein, mineral and vitamin intakes are maintained.

3. Liberal fluid intake is encouraged during the first five months. Subsequently, the intakes of fluid and salt are governed by the patient's ability to eliminate these, as indicated by urine output, weight gain, and edema. This has meant moderate to sharp restriction of water and sodium chloride during the last trimester of pregnancy in a number of patients.

4. Regular adequate sleep (nine hours) and gradually increasing periods of bed rest during the day as pregnancy advances are prescribed. In many instances, this comes to mean complete bed rest or hospitalization for some days or weeks in the latter months of pregnancy.

5. All foci of infection, such as abscessed teeth, are removed in the first five months of pregnancy. During the latter months, all such foci which are acute or subacute or which in our judgment may be aggravating the patient's condition are removed.

6. All hypertensive patients are seen in the clinic at intervals varying from not longer than one week to two to three days throughout pregnancy. They are also visited in the homes by the community health nurse between clinic visits.

7. The importance of prompt reporting of edema and classical symptoms of preeclampsia is impressed upon each patient. On the appearance of signs or symptoms, significant increase in blood pressure, albuminuria, sudden weight gain or edema, the patient is admitted to the hospital. If the signs and symptoms fail to improve or increase under hospital treatment, termination of pregnancy is considered with due regard for the maturity of the baby, the condition of cervix and the cephalopelvic relationship.

In this group of 105 patients with viable babies, labor was induced in 34 instances. Cesarean section was performed 7 times and pelvic induction either by castor oil alone or combined with artificial rupture of the membranes in 27 cases. The bag was rarely used.

The fetal mortality for all of the 122 hypertensive patients, including therapeutic abortions, was 21.9 per cent. Among the 105 patients whose babies reached viability

*Formerly we obtained daily catheter specimens from patients who were under observation in the hospital for the study of hypertension and albumin. After frequently repeated catheterization of patients at bed rest, pus was often found in previously normal urine sediment, and was occasionally followed before or after delivery with urinary tract infection. For several years we have limited catheterizations of patients at bed rest to the minimum number necessary for diagnosis. The meticulously obtained clean voided specimen has served for routine purposes without the risk of introducing the element of infection.

(over two pounds), there were 8 stillbirths and 2 neonatal deaths, a mortality of 9.5 per cent. It is of interest that 8 of the 10 babies lost were stillbirths. This suggests that in retrospect some of these babies might have been saved by somewhat more frequent induction of labor in patients near term.

From study of the clinical courses of these patients who began pregnancy with elevated blood pressures, the following observations may be made:

1. In 63 per cent the hypertension was aggravated at least temporarily during the latter months of pregnancy. In a considerable proportion of our patients in this group, we have observed a rather striking temporary decrease in the level of the blood pressure during the middle trimester, as shown in Fig. 1. This is an exaggeration of the slight decrease in blood pressure characteristic of the middle trimester in normal subjects. This is an important point to consider, for it demonstrates the fallacy of accepting as normal a large group of patients who first report during the fifth and sixth months of pregnancy with blood pressures within normal limits.

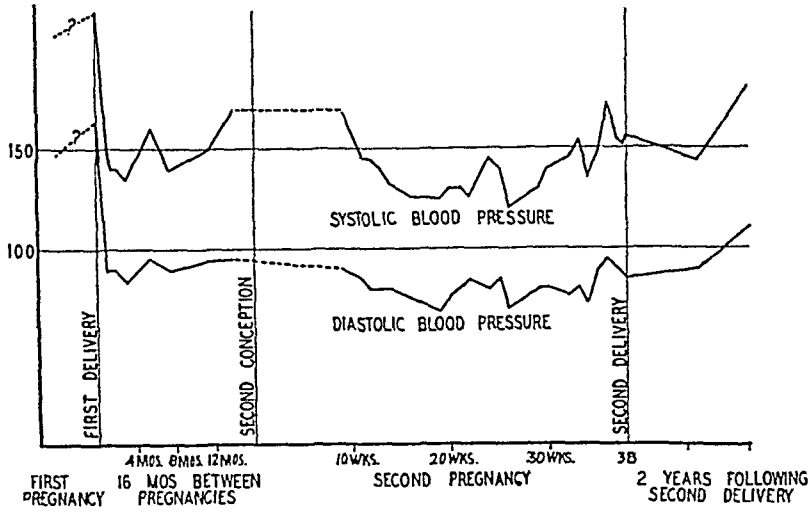


Chart 1.—The blood pressure of a patient with hypertension before, during, and after pregnancy.

This patient was first seen at the age of 39 in the thirty-eighth week of her first pregnancy, with a history of hypertension from the first trimester. On admission, the blood pressure was 200/165; the urine had a specific gravity of 1.030, 4 + albumin, hyalin and granular casts. The blood nonprotein nitrogen and urea clearance values were normal. Eye grounds showed retinal vessel sclerosis, hemorrhages, and exudate. She was delivered by cesarean section of a live baby. Mild hypertension with a normal urine, persisted for sixteen months until the second pregnancy. The record of her blood pressure during the course of the latter pregnancy is shown above. In the thirty-eighth week she was delivered by repeat cesarean section.

This chart shows a fairly characteristic exaggerated decrease in both systolic and diastolic blood pressures during the middle trimester of pregnancy although the subsequent rise during the last trimester is often more marked than in this patient.

2. In 70 per cent albuminuria appeared. In more than half of these, the amount of albumin was in excess of 0.6 gm. per liter. In addition, a considerable number of these patients developed marked edema. It is our impression that the frequent increase in blood pressure, appearance of marked albuminuria, sudden weight gain, and edema indicate that a considerable number of these patients superimpose preeclampia upon hypertension. Indeed, two patients developed typical eclamptic convulsions.

There were two maternal deaths in this group, one of which was due to amoebic dysentery and occurred three weeks post partum. The immediate cause of death was a gastrointestinal hemorrhage. The other death was in a patient seen with moderate hypertension and normal urine in the fourth month of pregnancy who left the clinic against advice. She was readmitted to the hospital four months later with antepartum eclampsia from which she died.

Of these 122 hypertensive patients, two, previously reported, died in the hospital. Three others are known to have died subsequently of hypertension. The remaining

117 have been subsequently studied. Of 89 patients followed for six months to three years after delivery, 44 per cent have blood pressures higher than when first seen. The remaining 28 patients have been followed for more than three to twenty years after delivery. The blood pressure is higher than when first seen in 20 of these latter 28 patients. These incidences of increase in blood pressure level, both in the groups followed for the shorter and the longer periods, might be expected in similar hypertensives irrespective of pregnancy. If pregnancy permanently accelerates the progress of hypertensive disease, its effect should be evident within two or three years post partum.

The urine of only 4 of these patients contained albumin at follow-up examination. In three of these instances, the urea clearance was normal. In the fourth, although the urine concentrated to 1.028, there were occasional red cells and a small number of hyalin and granular casts.

II. PATIENTS WHO WERE KNOWN TO HAVE HAD PARENCHYMATOUS NEPHRITIS BEFORE PREGNANCY

In this report we shall present only those patients with glomerulonephritis. Patients with acute and chronic pyelonephritis will be presented elsewhere in a study of urinary tract infection and pregnancy.

We have adequate records upon 15 patients who began pregnancy with known past records of acute or subacute glomerulonephritis. In 11 of these, we have a reasonably complete medical record from the date of onset of the acute or subacute nephritis from one to sixteen years before the pregnancy concerned. The acute episode in each instance was relatively prolonged and severe. All showed albuminuria of some degree and varying numbers of red blood cells and casts in the urine from the beginning of pregnancy. In general, the blood pressures in this group have been characterized by relatively more rise in diastolic than systolic tension. At the onset of pregnancy, they ranged from normal to 160/100. The diastolic pressure in most instances ranged from 90 to 100 mm. Hg. No therapeutic abortions were performed.

The regimen upon which these patients are managed during pregnancy is similar to that for the hypertensives. In 7 of them, the albuminuria increased as pregnancy advanced, and in 8 the blood pressure increased. One patient delivered a macerated nonviable fetus in the sixth month of pregnancy. The remaining 14 all delivered live viable babies, none of which died. Labor was induced in 7 instances during the last six weeks of pregnancy. None of the babies weighed over seven pounds.

The moderate increases in hypertension and albuminuria which we observed in these nephritic patients were not usually associated with sudden weight gain, development of edema and shifts of body water which frequently occur in simple pre-eclampsia and in many patients whose hypertensive disease is aggravated during the last trimester of pregnancy. In only one instance was there an explosive episode characterized by sudden marked increase in blood pressure, heavy albuminuria, oliguria, marked edema and symptoms. This patient, a primipara of 36 years, developed a classical picture of severe pre-eclampsia and had an attack of cardiac asthma with acute pulmonary edema. After preliminary digitalization and dehydration, she was delivered by cesarean section with recovery.

We have been surprised upon study of this group of patients to learn that they seemed to tolerate pregnancy well, and that classical pre-eclamptic signs and symptoms were relatively infrequent. To be sure, most of them did not show renal insufficiency at the onset of pregnancy. However, that pregnancy may be tolerated in the presence of relatively severe chronic glomerulonephritis may be illustrated by the history of one patient.

A tertigravida of 21 years was studied from the ninth week of her third pregnancy. The two previous pregnancies had been complicated throughout by albuminuria; and chronic nephritis had been diagnosed in another clinic between pregnancies.

The physical examination on admission was essentially negative except for moderate pallor. Laboratory findings were as follows: Blood: Hemoglobin 60 per

cent, nonprotein nitrogen 39 mg. per cent. Urine: Maximum gravity 1.012, albumin 3+, sediment occasional R.B.C. and W.B.C. The phenolsulphonephthalein test showed 48 per cent excretion in one hour. This patient was kept in the hospital until labor was induced by rupture of the membranes in the thirty-seventh week of pregnancy because of slight vaginal bleeding from a small premature separation of the placenta. She was delivered normally of a 5.5 pound baby who survived. The behavior of her blood pressure and renal function as pregnancy advanced is shown in Table I.

TABLE I

WEEKS PREGNANT	BLOOD PRESSURE	BLOOD			URINE				
		N.P.N.	R.B.C.	Hg	ALB.	CONC.	R.B.C.	CASTS	W.B.C.
10	106/ 76	39	3,450,000	65%	3+	1.010			
14		42	3,690,000	65%	3+	1.015	+	0	+
20	100/ 70	34	3,400,000	70%	2+	1.007	+	0	+
26	98/ 70	49			2+	1.009	+	0	+
31	106/ 62	46	3,010,000	60%	3+	1.010	+	++	+
33	118/ 70	48	3,400,000	60%	2+	1.010	++	+	0
37(del)	150/	52			3+	1.012	+	+	+
P.P. 1 wk.	118/ 78				4+	1.013	+	+	+
P.P. 2 wk.	120/ 84	57			4+	1.011	+++	+	+
P.P. 3 wk.	168/110	63			4+	1.014	+++	++	0
P.P. 4 wk.	138/ 88	43			4+	1.011	+	+	+
P.P. 9 wk.	118/ 88	61			4	1.014			

It will be observed that the specific gravity of the urine in concentration tests was consistently 1.015 or under, and that the nonprotein nitrogen was consistently above normal over a period of more than five months. The blood pressure increased slightly to 150 systolic at term, and the clinical prenatal course was uneventful except for three episodes of epistaxis. The post-partum course was uneventful for three weeks. Then the patient had an exacerbation of her glomerulonephritis with some urinary retention, elevation of blood pressure and rise in nonprotein nitrogen to 63 mg. per cent. This subsided after she had been symptom-free and about the ward for several days. She was discharged nine weeks post partum with blood pressure 118/88, light trace of albumin and nonprotein nitrogen 61 mg. per cent.

This patient illustrates the most severe degree of chronic kidney damage which we have followed throughout pregnancy. She illustrates to us the extreme limit of chronic glomerulonephritis which is compatible with the successful termination of pregnancy from the standpoint of the baby.

We were also surprised that there were not more cases of severe chronic glomerulonephritis complicated by pregnancy. Pregnancy seems to be frequent enough with severe hypertensive disease, but whether the incidence of sterility is high in patients with severe chronic glomerulonephritis, we can only surmise.

Follow-up examinations of these patients from six months to five years following delivery showed that four of them are essentially in worse condition than prior to the onset of pregnancy. The only patients whose conditions are bad are two. One of these, the patient in whom pre-eclampsia with acute pulmonary edema was superimposed upon her nephritis, has marked hypertension, albuminuria, edema, and symptoms. It is our impression that there may be a considerable vascular element involved in her condition. The patient whose case history is reported in detail is at present in a hospital under treatment for her nephritis. However, it should be pointed out that she was on the edge of renal insufficiency at the onset of pregnancy.

We do not wish to make light of the hazards of pregnancy to the glomerulonephritic. That there were no therapeutic abortions in this group is not due to our reluctance to perform therapeutic abortion upon glomerulonephritic patients.* In

*However, it would appear to us that the risk of pregnancy to the pyelonephritic patient is considerably greater, both from the standpoint of acute exacerbation and permanent progressive renal damage. The physiologic changes in the urinary tract incident to pregnancy favor exacerbation and progression of pre-existing pyelonephritis. For this reason, we are inclined to be more radical in advocating therapeutic abortion in the pyelonephritic patient.

several instances our information was not obtained until late in pregnancy, and in two, religion forbade therapeutic abortion. However, most of these patients tolerated pregnancy better than we had anticipated.

We are inclined to the belief, after study of the hypertensive as opposed to the glomerulonephritic group, that vascular disease is a considerably more common underlying factor in pre-eclampsia and eclampsia than is glomerulonephritis.

III. PATIENTS WITHOUT HISTORY OF ACUTE OR SUBACUTE NEPHRITIS WITH NORMAL BLOOD PRESSURE AND URINE PRIOR TO AND IN THE FIRST TRIMESTER OF PREGNANCY

These patients are the only ones of whom we are reasonably certain that the elevation of blood pressure, albuminuria, edema, and symptoms which developed in the latter part of pregnancy were uncomplicated by pre-existing vascular or renal disease. We have chosen to call those with milder disturbances pre-eclamptics, Grade I, and those with marked signs and symptoms pre-eclamptics, Grade II. We share the common point of view that only a certain number of patients in this general group are likely to have convulsions even if untreated, and that many of them, particularly in the milder group, will go on to uneventful delivery of a live baby at term, irrespective of treatment. Further, we believe that the vast majority of patients who are likely to develop eclampsia if untreated fall into the severe group, as subsequently defined. However, in dealing with any single patient, we know of no infallible means of prognosticating the outcome in this respect. Every year we are confronted with one or two patients with slight ante-partum hypertension and albuminuria without symptoms who unexpectedly develop intra-partum or post-partum convulsions. Conversely, we see a number who, on the basis of the severity of their signs and symptoms, might be expected to have convulsions and do not. The amount of hypertension, albuminuria, and edema are, of course, generally helpful, as is the level of uric acid in the blood. However, clinical methods are far from infallible in differentiating the potentially eclamptic cases. The interesting experiments of Dieckmann[3] concerning the variation in response of the blood pressure and urine output to small doses of pituitary extract in such cases offer a possible means for more precise classification. However, the method is hardly applicable as a routine clinical test because of the reactions which are sometimes encountered, especially in the potentially eclamptic group.

Thus, we would justify the tentative use of the term pre-eclampsia, Grade I, in the milder cases, for some of these patients, at least, are potential eclamptics. That many others may be patients with latent hypertension is suggested by clinical and follow-up study of the group.*

a. Pre-eclamptics, Grade I (Mild).—There are 235 patients in this group, all of whom had some elevation of the blood pressure in the last trimester of pregnancy. The range of systolic pressure was usually from 140 to 160 mm. Hg, and the diastolic pressure generally ranged from 90 to 100 mm. Hg. The urine contained not more than 0.6 gm. of albumin per liter and edema was variable, usually slight or absent. Patients who had symptoms which are generally recognized as indicating that convulsions are imminent, such as severe frontal headache, blurred vision and amblyopia, epigastric pain, vomiting, torpor and irritability were not included.

*Retinoscopy is of considerable value as a guide to policy in the treatment of patients with hypertension and albuminuria complicating pregnancy. However, we have found it of little value in the differential diagnosis between mild hypertensive disease and mild pre-eclampsia. Follow-up study has shown that we are unable to differentiate between the early structural change of the retinal vessels characteristic of hypertensive disease and spasm. In the group of 235 patients classified as pre-eclampsia, Grade I, there were many with subsequent hypertension whose retinal vessels were normal at the time of the pre-eclampsia. Of greater significance is the fact that there were 16 patients upon whom the diagnosis of mild to moderate retinal vessel sclerosis was made who subsequently showed repeatedly normal blood pressures. Family history for hypertensive disease as obtained from clinic patients is unreliable. The patients with post-partum hypertension were equally divided with respect to positive and negative family histories for hypertension, while 34 patients who gave positive family histories subsequently had normal blood pressures. Family histories controlled by taking the blood pressures of parents and siblings have been of definite significance in a small series of cases.

The measures used in the treatment of these 235 patients were usual ones. They consisted of rest, light diet with adequate protein and low salt intake, mild saline catharsis when indicated, and restriction of fluid intake which was adjusted to the individual's ability to eliminate water. Most patients of this group were in the hospital for three or more days prior to delivery.

Cesarean section was performed upon 12 patients, but in no instance primarily because of the toxemia. Labor was induced by castor oil alone or combined with artificial rupture of the membranes in 76 patients or 32.54 per cent.

There were no maternal deaths. The fetal mortality was 4.8 per cent, and it is of interest that all babies lost were viable stillbirths. Further, no stillbirths resulted from labor induction. Although the total fetal mortality was relatively low, this stillbirth rate is some three to four times that for the hospital, exclusive of toxemics. It has become well established that liveborn babies of more than thirty-six weeks gestational age rarely succumb to prematurity. With this in mind, it might be well to consider more frequent inductions of labor during the last four weeks of pregnancy in all types of so-called pregnancy toxemias.

We have examined the patients of this group at intervals of from six months to three years post partum. There were no instances of detectable impaired renal function. The incidence of systolic blood pressures above 150 mm. Hg was 21 per cent, although the average age at the last examination was less than thirty years. This is some three times the incidence of hypertension for women of similar age distribution, irrespective of pregnancy toxemia, and as will be shown, greater than for the group with severe uncomplicated pre-eclampsia (Grade II). These observations might be used in support of our impression that the group above defined as pre-eclamptics, Grade I, contains a number of patients with latent hypertension made manifest by pregnancy.*

b. Pre-eclamptics, Grade II (Severe).—This group is made up of 50 patients, all of whom developed sustained systolic blood pressures over 160 mm. Hg. In most instances, the diastolic pressure was over 110 mm. Hg. All of them excreted more than 0.6 gm. of albumin per liter of urine. The amount of edema was variable, although it was marked in most cases. Most of these patients had one or more of the premonitory symptoms of impending eclampsia, such as severe frontal headache, blurred vision or amblyopia, epigastric pain, vomiting, torpor, or irritability.

All of these patients were under observation in the hospital prior to delivery. In general, therapeutic measures consisted in absolute bed rest, sharp restriction of water and salt, light diet and moderate saline catharsis. A number of them were given morphine or sedatives, and some were digitalized and given magnesium sulphate intravenously. There were five instances of premature separation of the placenta and five twin pregnancies.

Pregnancy was terminated prematurely in 40 patients. This was accomplished by cesarean section in 15, and pelvic induction of labor in 25 instances. The gross fetal mortality was 25.5 per cent. Of the 55 babies delivered, 10 were stillborn of whom 7 weighed more than four pounds. There were 4 neonatal deaths of premature babies. Forty-one babies were discharged living and well. There were no maternal deaths in this group.

*In addition, 83 patients who had had pre-eclampsia as defined, three to eighteen years before, have been studied from the standpoint of subsequent hypertension and cardiac enlargement. The average age at the time of follow-up examination was 35.5 years. The incidence of systolic pressures over 150 mm. Hg was 44.6 per cent, and the transverse diameter of the heart exceeded one-half the transverse diameter of the chest in 36 per cent. In a control group of parous women delivered during a corresponding period, with a similar age distribution, whose pregnancies were known to have been uncomplicated by hypertension or albuminuria, the incidences of hypertension and cardiac enlargement were 7 per cent and 14 per cent, respectively.

These relative incidences of hypertension are of interest. Not only is the incidence of hypertension following pre-eclampsia, Grade I, more than three times the average for women of similar age distribution irrespective of pregnancy, but also those women who have had pregnancies uncomplicated by pre-eclampsia show an incidence of hypertension subsequently which is considerably below that for women of similar age distribution, irrespective of pregnancy.

This latter observation suggests that the ability to go through pregnancy without rise in blood pressure is an excellent test for the absence of latent hypertension.

Forty-seven of these severely pre-eclamptic patients have been examined from six months to two and one-half years following delivery. One patient had both hypertension (blood pressure 170/110) and a very slight trace of albumin in the urine one year post partum. This woman is an octipara, 41 years of age. We have been unable to persuade her to come in for more complete study. There are 5 additional patients who have had systolic blood pressures between 140 and 155 on one occasion after the third month post partum. In each instance at one or more subsequent visits, the blood pressure has been less than 140 mm. Hg. Thus, of 47 patients with severe pre-eclampsia who have been followed for six months to two and one-half years post partum, only one has definite hypertension or albuminuria.

IV. PATIENTS ABOUT WHOM THERE WERE INSUFFICIENT DATA CONCERNING THE VASCULAR AND RENAL SYSTEM BEFORE PREGNANCY TO PERMIT OF EXCLUDING ANTECEDENT VASCULAR AND RENAL DISEASE

There are 185 patients who fall into this group. Many of them were first examined after the fifth month of pregnancy and had no reliable records of blood pressure or urine examination prior to this visit. A number showed blood pressure readings well within normal limits and narmal urine at two or three visits during the middle trimester of pregnancy, followed by the appearance of hypertension with or without albuminuria and edema. We have no doubt that some of these, if we had adequate records, would fall into the previously defined pre-eclamptic groups. However, we do not have such records. There are also a number of patients upon whom we have records of blood pressure beginning in the fifth and sixth months of pregnancy which ranged from 130 to 140 mm. Hg systolic over 85 to 90 mm. Hg diastolic, who subsequently showed definite hypertension with or without albuminuria. We believe that many of these were definite hypertensive patients whose blood pressure had decreased temporarily during the middle trimester to within normal limits. As we have previously pointed out, the characteristic decrease in blood pressure in the middle trimester of pregnancy seen in normal patients is often exaggerated in hypertensive patients. There are also undoubtedly a few parenchymatous nephritic patients included in this group.

The clinical courses of the majority of these patients were similar to those of the group described under pre-eclampsia, Grade I. Twenty-eight of them, had they been known to have been normal prior to pregnancy, would have been classified as pre-eclamptic patients, Grade II. However, the fetal mortality for this whole group was 6.5 per cent, a rate which approaches that of the known hypertensive patients. At follow-up examination, 93 of these patients showed systolic blood pressures of over 150 mm. Hg, an incidence of 50 per cent.

DISCUSSION

Our principal objective has been to divide the patients into clearly defined groups, the study of which will give us an improved basis for offering both an immediate prognosis for pregnancy with respect to the mother and baby, and an ultimate prognosis for the mother with respect to subsequent vascular and renal disease. In addition, such study would seem to give information of value with respect to the question whether pregnancy toxemia initiates a progressive vascular hypertensive process. We are aware that the method of classifying patients is not ideal. However, it has the advantages that it is primarily descriptive and that it involves the use of no new terms.

The results of this study are in accord with the general opinion that pregnancy should be avoided by patients with marked vascular hypertension. Evidence of structural changes in the vessels of the retina, vascular symptoms, cardiac enlargement, evidence of renal damage, and finally, the lack of response of the blood pressure, particularly the di-

astolic pressure, to a few days of bed rest characterize the poor risks in the hypertensive group. When early pregnancy is found in patients of this type, we believe that therapeutic abortion is indicated.

On the other hand, patients with mild asymptomatic hypertension, which decreases considerably with bed rest, no cardiac enlargement, normal urine and renal function have a 90 per cent chance of obtaining a live viable baby, provided that they are under a strict hygienic and nutritional regime. We would point out that even in this group, the hypertension increases during the last trimester of pregnancy in over half of the cases, and that marked albuminuria appears in nearly half. At follow-up examination, the blood pressure was found to be significantly higher than before the pregnancy under consideration in 53 per cent of the cases. However, in a few instances it was lower, and in many it was unchanged. Further, each time we are almost convinced that pregnancy permanently aggravates hypertensive disease, we see three or four women whom we know to have had hypertension for years at follow-up examination, who show no evidence of progression after a long series of pregnancies. Certainly, we do not find enough evidence to justify radical interference in patients already pregnant, with mild asymptomatic hypertension, normal hearts and kidneys.

With reference to patients with chronic glomerulonephritis, our group is too small to justify a definite opinion. Having obtained 14 living babies from 15 patients we are inclined to be less pessimistic about the immediate outcome with respect to the baby than previously. We shall tentatively take the position that in the absence of history of signs of renal decompensation, the wishes of the patient may be weighed with reference to continuing an existing pregnancy.

Among the patients known to have been previously normal who developed hypertension with or without albumin and edema during the last trimester of pregnancy (pre-eclampsia, Grades I and II), it is of considerable interest that subsequent hypertension was much more frequent in the mild than in the severe group. The data presented lend support to the premise that in many patients of the mild group, the terminal appearance of asymptomatic hypertension is the response to pregnancy that one may expect in individuals with latent hypertension. This is in agreement with the view expressed by Herrick and Tillman.[4] However, at present we know no practical clinical means of differentiating the potentially eclamptic patients of this group from the others. We cannot entirely agree with Stander[5] that such individuals can do themselves no harm by successive pregnancies. If one-fifth of this group can date the onset of their hypertension from one pregnancy alone, it would appear that one should be cautious in subjecting this group to the insults associated with repeated pregnancies.

Finally, from the evidence we have been able to obtain regarding previously normal patients who developed marked albuminuria, hypertension, edema, and symptoms in the last trimester of pregnancy, commonly described as eclampsism (our pre-eclampsia, Grade II), the sequelae referable to the vascular and renal systems appear to be minimal. The commonly held viewpoint that this disease frequently

causes permanent and progressive vascular or renal damage is not substantiated by our data. Our findings in this group are consistent with our previously reported experience with a similar group of previously normal individuals who had had eclampsia. The two seem to be the same disease except for the added symptoms of convulsions and the attendant poorer immediate prognosis in eclampsia. The greater incidence of subsequent hypertension in the group of previously normal patients who developed mild asymptomatic hypertension with or without albuminuria (pre-eclampsia, Grade I) suggests that many of them suffered from latent hypertension made manifest by pregnancy, rather than a milder form of our pre-eclampsia, Grade II. However, until some satisfactory clinical means of identifying these patients with latent hypertension during pregnancy is devised, we feel obliged to include them in the group designated pre-eclampsia, Grade I.

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CIRCUMVALLATE PLACENTA IN UTERO

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In view of the clinical significance of circumvallate placentas, recently emphasized by Hobbs and Rollins,[1] Goodall,[2] and Hunt,[3] the report of a circumvallate placenta in utero seems pertinent. Granting that discrepancies in the reported frequencies of delivered circumvallate placentas may be due in part to a failure to discriminate between marginate and circumvallate types, it is nevertheless obvious that the opportunity to observe either of these related types in utero is exceptional. Herff,[4] in 1896, definitely stated that no circumvallate in situ had been described. Liepman[5] later reported four uteri in which folds of membranes projected into the amniotic cavity and overlapped the placental margin to a greater or lesser extent. Meyer[6] described a four-months pregnant uterus with a marginate placenta in utero. Bumm[7] pictured a circumvallate and a marginate placenta in utero.

Gross Specimen.—This was removed therapeutically from a tuberculous patient at about the fifth month of gestation (the fetus measuring 14 cm. crown-rump). The uterus was first fixed intact in 10 per cent formalin, then after hardening it was divided in two slightly unequal parts, a posterior section representing 42 per cent of the total uterine surface, and an anterior, 58 per cent.

The placenta covered the greater portion of the posterior section, beginning about 3 cm. above the internal os and extending about 1.5 cm. into the superior portion of the anterior section (Fig. 1). For this stage of gestation, the placenta covered relatively a small extent, 36 per cent of the entire uterine lining.

The uterus, almost spherical in form, measured 13 cm. in its greatest length (from internal os to outer surface of fundus), in maximum transverse breadth 13.7 cm. and 12.2 cm. anteroposteriorly. The thickness of the uterine wall varied in different locations, averaging 0.55 cm.

The placenta presented all the characteristics of a typical circumvallate form as described by Williams.[8] The cord was attached near the center of the placenta, the distance between its insertion and the placental rim fluctuating between 4.5 and 5.8 cm. Radiating in all directions from the base of the cord, the umbilical vessels ramified beneath the amnion. Before reaching the ring formation, however, the branches turned directly into the substance of the placenta, the ring thus being devoid of superficially coursing vessels.

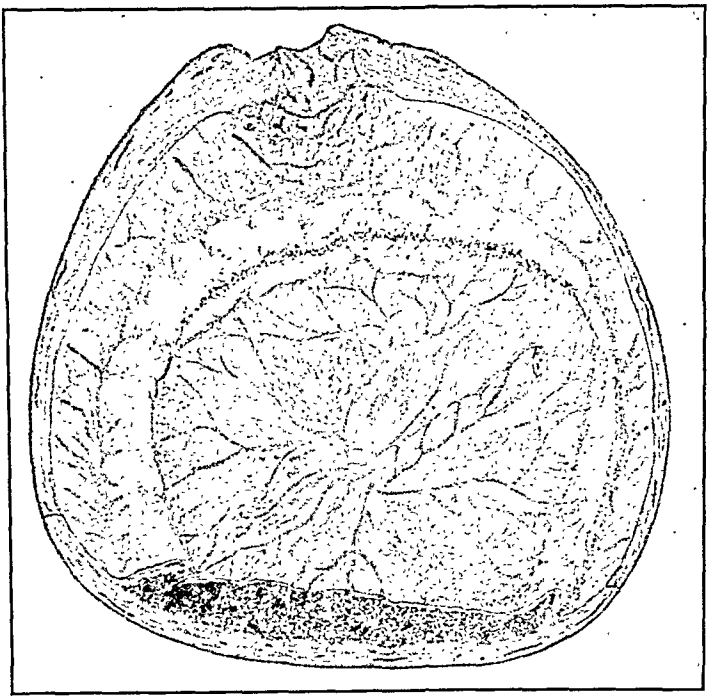


Fig. 1.—Circumvallate placenta in utero.

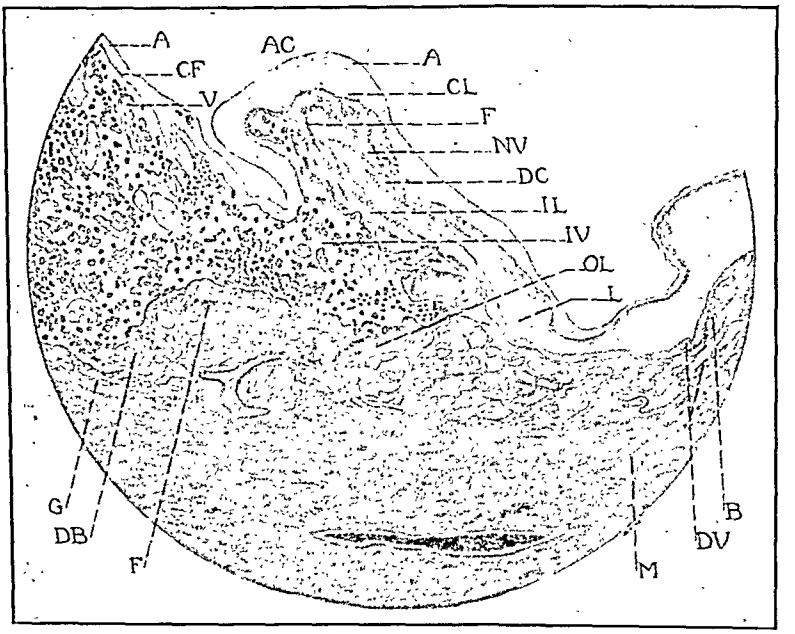


Fig. 2.—Fold and adjacent structures of a circumvallate placenta, drawn at 10× magnification. *A*, amnion; *AC*, amniotic cavity; *B*, blood vessel; *CF*, chorion frondosum; *CL*, chorion laeve; *DB*, decidua basalis, proper; *DC*, decidua capsularis; *DV*, decidua vera, proper; *F*, fibrin; *G*, uterine gland; *IL*, inner lamella of extrachorial placenta, decidua vera; *IV*, intervillous space; *L*, uterine lumen; *M*, myometrium; *NV*, necrotic villi; *OL*, outer lamella of extrachorial placenta, decidua basalis or vera(?); *V*, villi.

The ring, which encircled the entire placenta, varied in width and form. The actual ring, yellowish white in color, appeared as a thickened, elevated ridge, as a vertical fold, or as a centrally reflected horizontal shelf (Fig. 1). The ledge or free part of this flattened fold was composed of two layers each of amnion and chorion with the related decidua (Figs. 2 and 3). The slit-like space between the fetal surface of the chorial-placenta and this amniochorial duplication varied in width. The amnion, chorion laeve, and decidua capsularis were reflected peripherally from the inner border of the rim or ledge, covering the ring as they were directed toward the region of decidua vera (Figs. 1 and 2).

Microscopic Examination.—A microscopic study was made in the region of the amniochorial duplication. A section of the duplication (Figs. 2 and 3) showed, in order from within outward, amnion, chorion laeve, decidua capsularis, a space (limited centrally by a confluence of decidua capsularis and vera), decidua vera (?), chorion laeve and amnion. Then follow in order the tunnelled or slit-like extension of the amniotic cavity, the amnion, chorion frondosum, decidua basalis (or split vera), and myometrium.

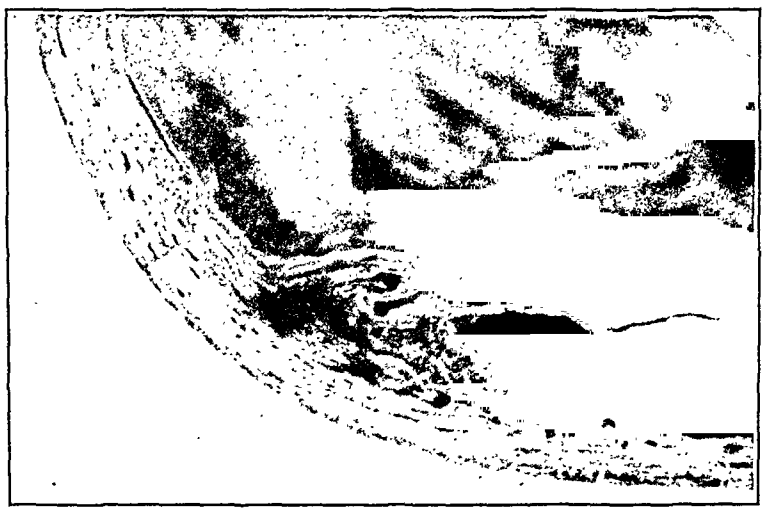


Fig. 3.—Photograph of gross specimen from which the block was removed for drawing, Fig. 2.

The ring itself was composed of rudimentary villi, degenerating decidual cells, necrotic cells (lymphocytes and fibroblasts), "phantom" red blood corpuscles and an abundance of fibrin. At the inner border of the ring (instead of from the periphery of the placenta as normally), the decidua capsularis became continuous with decidua vera which was split in two layers by the chorionic villi and intervillous space. The lower or outer layer was continuous with the decidua basalis; the upper or inner layer formed the extrachorial covering of the placenta and was continuous with the capsularis. The decidua capsularis, thickened at the junction with the decidua vera, became greatly reduced as, with the amnion and chorion laeve, it extended peripherally from the ring, separated from the extrachorial placenta by a definite space. The villi of the chorion laeve did not terminate abruptly; instead, small rudimentary stems extended from the chorionic plate for a short distance (approximately 1.5 mm.) beyond the confluence of the two lamellae of decidua vera. Interspersed among these degenerating villi there were clumps of cells of uncertain identity. They were definitely either trophoblastic or decidual, but a discrimination was impossible at the present time.

Composed of only a few cells and much fibrin at the ring, the capsularis showed a progressive reduction in thickness and increased necrosis from the ring outward. It was entirely wanting on the wall of the uterus opposite the placental attachment. The lamellae of the extrachorial placenta showed marked fibrin precipitation facing the villi. The intervillous space separating the vera into two layers was continuous for some distance beyond the placenta with the maternal blood vessels of the decidua vera, the extended extrachorial intervillous space having apparently utilized the vessels of the decidua vera (Fig. 2).

The decidua basalis and basal lamella of decidua vera presented a compact and a spongy layer (Fig. 2). The inner lamella of the extrachorial decidua vera was composed almost entirely of compact decidua. In the vicinity of the extrachorial placenta, beginning at the inner free edge of the fold and extending just beyond the extrachorial margin, the uterine glands were greatly augmented, thereby increasing the thickness of the decidua. The extremes of the thickened decidual zone were 2.6 mm. and 1.3 mm., the compact constituting 0.4 mm. and 0.8 mm., respectively. Immediately centralward from the ring, the decidua was practically reduced to a spongy layer which measured only 0.3 mm. in thickness. Further centrally the decidua basalis measured 1.3 mm. with compact and spongy layers about equally divided. The vera adjacent to the extrachorial placenta measured 1.6 mm., of which the spongy layer alone amounted to 1.2 mm., but further removed from the placenta, the decidua was thin, measuring approximately 0.5 mm., with the spongy layer constituting about four-fifths of the entire thickness.

Theories of Origin.—Williams reviewed so thoroughly the literature of the many conflicting theories of origin of circumvallate placentas that only those not included in his publication are reviewed here. Drosin[9] states that placental rings, which he

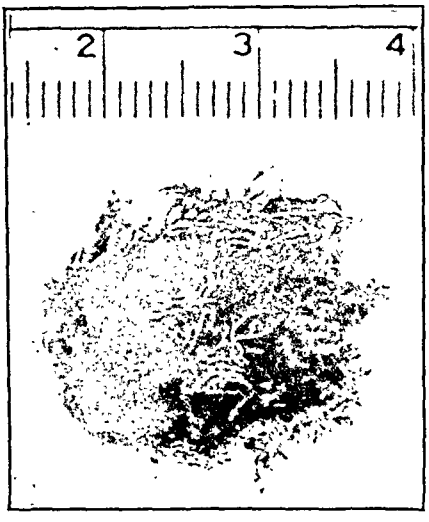


Fig. 4.—Photograph of an early chorionic vesicle.

considers identical in nature and origin with typical forms of circumvallate, represent evidence of readjusted prenatal separation of placenta. Kreis[10] considers that margination is due to hemorrhage which results in fixation of chorion with or without folds. Manzi[11] feels that circumvallate placentas and cysts are accompanied by fibrinous deposit following hemorrhage during pregnancy. Talbot[12] associates the circumvallate formation with chronic sepsis during pregnancy, stating that persistent growth of placental tissue from the maternal surface within the injured edge raises the infarcted edge and the margin of the attached membranes away from the uterine wall, resulting in typical circumvallate formation. Goodall ascribes circumvallation to chorionic sclerosis following reactionary edema; this sclerosis of the chorion is supposed to diminish its expansibility, hence resulting in the hypertrophy of placental tissue beyond the infarction. Corinaldesi,[13] while supporting Sfameni's[14] idea of in-co-ordination in distention of the uterus and placental growth, as well as variation in uterine and intrachorionic pressure, mentions a functional theory of Funck[15] wherein the extrachorial margin is regarded as an expedient reduction of excess placenta. Torpin[16] favors a similar mechanism: "placenta marginata and placenta circumvallata are the results of the effort of nature to convert excess placental tissue into passive membrane." He further states that circumvallate placenta forms when the ovum is embedded in the uterine cornu ("Tubenecke Placenta" of Bayer[17]) and others.

Hobbs and Rollins agree with Meyers, Williams and others in the manner of formation of circumvallate placenta. That also is the interpretation supported by the present writer.

In the absence of tangible evidence concerning implantations, it is impossible to determine conclusively the etiology of these circumvallate placentas. However, it is suggested that the large villous roots, with their many small branches dispersed through a relatively small thick placenta (as observed by me[18] in circumvallate placentas) as well as the extrachorionic structural relations existing in the specimen here reported, are in accord with the theory expounded by Meyers and later by Williams, namely, that the immediate origin of the circumvallate placenta is from scanty development of the chorion frondosum. Chorionic vesicles of like age display wide variation in the extent of the chorion frondosum, and not infrequently its area is much reduced, as in the specimen shown in Fig. 4. Note that the frondosum is relatively small (actually smaller than the picture indicates as the specimen turned slightly while photographing); the villi are large, markedly elongated and greatly branched. Just what is responsible for this overzealous degeneration of villi over the remainder of the chorion is the pertinent question. Many factors may be responsible, as aptly pointed out by Goodall. Defects may be inherent in the ovum before fertilization or may arise after implantation due to disease or unfavorable condition of the uterine mucosa. Shute[19] reports spontaneous abortions with deciduas which are apparently normal, where the abortion is assumed to be due to "an elusive biochemical mechanism" involving the resistance of maternal blood serum to the activity of the trophoblast. These and many other factors determine the activity of the trophoblast, therefore, the size of the chorion frondosum, the ultimate size of the placenta and the possibility of the continuation of gestation.

The chorion begins its differentiation into chorion frondosum and chorion laeve in the second month of pregnancy. Once this distinction has occurred, it is irrevocable. As pregnancy advances the chorion frondosum and decidua basalis are uniformly extended. If the frondosum is too restricted to satisfy the developing individual, the pregnancy is either terminated or adequate absorptive area is secondarily established. To compensate for the reduced area, villi elongate, undergo marked branching and of necessity are diverted peripherally. (The lines of growth tension illustrated by Goodall in his Figs. 7 and 8 show such extension of villi beyond the frondosal plate.) In so doing these peripheral villi split the decidua vera, producing the condition observed in the extrachorial part of the placenta (Fig. 2). With the enlargement of the fetus, the extraplacental membranes at the limit of the frondosum would bend back on themselves as they fill the uterine cavity about the fourth month of pregnancy, thus forming the ring of the circumvallate placenta. Due to disturbance of the normal relations, including the altered blood supply at the fold, sclerosis is the natural sequence. The degree of distention or the general contour of the bulging ovum as it balloons into and fills the uterine cavity would determine the extent and character of the ring and membrane duplication. Sclerosis thus plays a secondary role in the ring formation.

It would seem, then, that whatever the underlying cause, circumvallate placenta is the result of too scanty development of the chorion frondosum.

I wish to thank Dr. J. Blaine for the drawings.

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Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

TENTH ANNUAL MEETING, MINNEAPOLIS, MINN.
OCTOBER 6, 7 AND 8, 1938

The following papers were presented:

Presidential Address—Pelvic Pain. Dr. Robert D. Mussey, Rochester, Minn. (For original article, see page 729.)

Three Hundred Cases of Extensive Conization of the Cervix. Drs. R. J. Crossen and G. J. L. Wulff, St. Louis, Mo. (For original article, see page 849.)

B. Welchii Infections in Pregnancy. Drs. P. B. Russell, Jr. and M. J. Roach (by invitation), Memphis, Tenn. (For original article, see June issue.)

The Clinical Significance of Endometriosis. Dr. V. S. Counseller, Rochester, Minn. (For original article, see page 788.)

Cystography in the Diagnosis of Placenta Previa. Drs. Robert J. Prentiss and Warren W. Tucker (by invitation), Iowa City, Ia. (For original article, see page 777.)

Arrhenoblastoma of the Ovary. Drs. A. E. Kanter and A. H. Klawans, Chicago, Ill. (To be published in American Journal of Cancer.)

The Use of Solutions of Acacia in Obstetrics. Drs. L. M. Randall and A. B. Hunt, Rochester, Minn. (For original article, see page 819.)

Ureteral Injuries in Gynecologic Surgery. Drs. M. L. Leventhal, Irving J. Shapiro (by invitation), and A. J. Platt (by invitation), Chicago, Ill. (For original article, see page 797.)

Myomectomy During Pregnancy. Drs. Ralph A. Reis and M. B. Sinykin (by invitation), Chicago, Ill. (For original article, see page 834.)

The Birth of an Influence. Dr. E. D. Plass, Iowa City, Iowa.

A Study of Suspended Human Muscle Strips in Vitro. Drs. Fred L. Adair and John A. Haugen (by invitation), Chicago, Ill. (For original article, see page 753.)

Collapse Therapy for Tuberculosis in Pregnancy. Drs. Ward F. Seeley, R. S. Siddall, and Walter J. Balzer (by invitation), Detroit, Mich. (For original article, see page 741.)

Prophylactic Endocrine Therapy in Surgical Menopause. Dr. Philip F. Schneider, Evanston, Ill. (For original article, see page 861.)

Do Eclampsia and Pre-Eclampsia Cause Permanent Vascular Renal Pathology? Drs. Wm. J. Dieckmann and Ira Brown (by invitation), Chicago, Ill. (For original article, see page 762.)

The Clinical Significance of Appendices Epiploicae. Dr. Howard C. Walser, Detroit, Mich. (For original article, see page 811.)

Statistical Analysis of One Thousand Abortions. Dr. Jalmar H. Simons, Minneapolis, Minn. (For original article, see page 840.)

The Effect of Alkaline Vaginal Douches on the Huhner Test and Sterility. Dr. J. Milton Singleton (by invitation) and Jean Lamar Hunter, Kansas City, Mo. (For original article, see page 856.)

Dührssen's Incisions. Dr. Carl P. Huber, Indianapolis, Ind. (For original article, see page 824.)

The Duluth Obstetrical Board. Dr. Russell J. Moe, Duluth, Minn. (For original article, see page 871.)

A Report of the Committee on the Induction of Labor. Drs. Roland S. Cron, Milwaukee, Wis., L. M. Randall, Rochester, Minn., and N. R. Kretzschmar, Ann Arbor, Mich. (For original article, see page 873.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Toxemias of Pregnancy

Glassman, Oscar: A Study of Hyperemesis Gravidarum With Special Reference to Blood Chemistry, Surg. Gynec. Obst. 66: 858, 1938.

All cases of hyperemesis gravidarum are classified as toxemia. The incidence in the Woman's Clinic of the New York Hospital is 0.71 per cent. The average age in this series is 27.9 years. There is an increased incidence in primiparas but no apparent increase in elderly primiparas. Hyperemesis gravidarum is relatively infrequent in negroes.

The length of time during which vomiting persists, the duration of the pregnancy, the pulse rate, and the blood pressure have no definite relation to severity of the condition.

High hemoglobin appears to be of some diagnostic significance and as a rule denotes marked dehydration.

The nonprotein nitrogen and the uric acid content may be increased but show a sharp drop after treatment with intravenous fluids. In some cases of late vomiting of pregnancy and in some patients who do not respond to treatment, the nonprotein nitrogen and the uric acid content tend to rise.

Blood chlorides and sugar values are usually within the normal limits. A few patients show extremely low values but respond to therapy.

There is a marked fluctuation in the carbon dioxide combining power of the blood with great tendency to acidosis.

Acetonuria is a conspicuous finding and although not the immediate cause of vomiting, control by proper therapy is important.

The value of blood chemical studies in the rational treatment of hyperemesis gravidarum is at once evident.

Prognosis is dependent upon the following: The hemoglobin values, the weight curve, the presence or absence of acetonuria, the blood chemistry determinations, and the effect treatment has on these factors.

Among the indications for interruption of pregnancy are continued loss of weight with rising nonprotein nitrogen and uric acid, retinal hemorrhages, and marked jaundice.

WILLIAM C. HENSKE.

Trillat, P., and Bernay, P.: Three Cases of Severe Vomiting of Pregnancy Treated by the Duodenal Tube With Biliary Drainage, Bull. Soc. d' obst. et de gynéc. 26: 213, 1937.

The authors treated three cases of hyperemesis gravidarum by means of the duodenal tube. This procedure enabled the patients to receive fluids, salt, and sugar, with insulin to overcome dehydration, chloropenia, inanition and acidosis. Above all it permitted biliary drainage which was instituted by the administration of huge doses of magnesium sulfate. These treaments were repeated every few days and the patients were cured after three or four passings of the tube.

J. P. GREENHILL.

Fischer, E.: Rectal Instillation of the Patient's Own Urine in the Treatment of Vomiting of Pregnancy, Med. Klin. 32: 1298, 1936.

During the last ten years numerous recommendations have been made for the treatment of hyperemesis gravidarum. These include the use of Lugol's solution,

bromides, corpus luteum, thyroid, serum from pregnant women, the patient's own blood and the serum of the patient's husband. Since Titus and Givens recommended the use of intravenous glucose, the author has used this with insulin.

Since 1931 among 12,207 labor cases the author encountered 141 cases of hyperemesis. Pregnancy had to be terminated in 26 cases or 18.4 per cent. One woman died.

In spite of the good results obtained by means of glucose and insulin, the author sought a new form of treatment. During the past year he has been using the patient's own urine and administering it in the form of a rectal instillation. In addition to this, the patient is almost starved during the first two or three days. The urine is administered twice daily, at first in 5 c.c. doses then with a daily increase of 1 c.c. until 15 c.c. are given twice a day. The patient is not told of the nature of the rectal instillation. In all 9 patients where this form of treatment was employed, the toxic vomiting ceased after three or four days. There were no recurrences of vomiting.

J. P. GREENHILL.

Baens, Alfredo, and Espinola, Noe: Acute Yellow Atrophy of the Liver in Pregnancy, J. Philippine Islands M. A. 17: 679, 1937.

The authors state that out of 53,129 patients admitted over a period of twenty-seven years, 6 cases were diagnosed as acute yellow atrophy of the liver. Most of the cases occurred during the last trimester of pregnancy.

The symptoms most commonly presented are those of severe toxemia, referable to serious disturbances of liver and stomach, the central nervous system, heart and kidneys. In a pregnant woman with some signs of a toxemia of pregnancy, the appearance of a subicteric tinge in the sclera should serve as a warning that more serious developments may follow. Vomiting is quite a common symptom, also severe pain in the epigastrium and in the region of the liver. The kidneys show signs of acute nephritis, with albumin, casts, and sometimes red blood cells in the urine. The patients had scanty and highly colored urine. Marked prostration and dyspnea are other common symptoms.

C. O. MALAND.

Hofbauer, J.: Pathogenicity of Eclampsia, Zentralbl. f. Gynäk. 61: 2482, 1937.

Hofbauer reviews his own contributions to the etiology of eclampsia. The pregnant organism is under the persistent influence of protein split products. The syncytial elements from the periphery of the ovum gain access to the intervillous spaces in the placenta and eventually into the maternal circulation, where they bring about necessary changes in the glands of internal secretion (anterior pituitary, thyroid, adrenals). He has demonstrated an increased hypophyseal-adrenalin effect which may be direct or indirect and has shown that there is an increase in the adrenalin content in the blood of eclamptic women.

There is an indirect parallelism between the findings in the blood of women with eclampsia and animals into which posterior pituitary extract has been injected intravenously. There is an aerobiosis of the tissues in animals after intravenous injections of pituitary just as there is in eclamptic organisms. There is also a generalized spasticity of the arterioles and an analogous change in the various organs of the body.

Hofbauer refers to Dieckmann's investigation of the effects of pituitary extract on nonpregnant, pregnant, and pre-eclamptic women. Dieckmann found a slight increase in the blood pressure of normally pregnant women after injection of pituitary, but there were a precipitous rise in blood pressure and an oliguria following injection of pituitary extract in the women who had pre-eclampsia. These findings support the theory of hormonal origin of the toxemias of the second half of pregnancy.

Hofbauer asks whether it is excessive production of pituitary and adrenal hormones or lack of removal of these hormones which is responsible for the toxemias. He points out that in order for neutralization of these hormones to

take place it is necessary to have intact liver function. On the other hand, an increased pituitary hormone content of the body harms the liver; hence there is a vicious circle. Hofbauer maintains that the increased effects of the posterior pituitary-adrenal system in eclampsia are due to lack of neutralization of these hormones in the liver and the capillary endothelium.

J. P. GREENHILL.

Shute, Evan: The Endocrine Background of the Toxemias of Late Pregnancy, Surg. Gynec. Obst. 65: 480, 1937.

The late toxemias of pregnancy may be grouped into two principal categories, those which are real or impending eclampsia, and those which are real or impending retroplacental hematomas or abruptio placentae. These groups may be differentiated by the fact that the former excrete a great excess of prolan and the latter are marked by an excess of estrogenic substance in the blood.

Similarly, studies of thyroid activity and of blood cholin values give further reason for such a fundamental division of the late toxemias.

The abruptio placentae type exceeds the eclamptic type by about nine to one in the small series studied. It was found that wheat germ oil is a prophylactic and therapeutic agent of great value in treating the abruptio placentae group.

There is some reason to suspect that estrin therapy may assist in the therapy of the eclamptic type.

WILLIAM C. HENSKE.

De Snoo, K.: Eclampsia and Premature Separation of the Placenta, Monatschr. f. Geburtsh. u. Gynäk. 102: 257, 1936.

In the opinion of the author the placenta produces not only specific hormones but also products of metabolism which are important during pregnancy. These metabolic products are not constant but change with advance in pregnancy. It is the latter products and not the specific hormones which produce intoxication symptoms during pregnancy. As yet these products are not determined, but they are the ones responsible for edema of the tissues, spasm of the blood vessels, and disturbances in the liver, kidneys, and circulatory system. They also produce changes in the brain which lead to eclamptic convulsions. The conditions necessary for the occurrence of eclampsia are retention of salt, increase in blood pressure, and increased sensitivity of the convulsion center. The exciting cause of eclampsia is some particular emotion such as fear, worry and hyperventilation. Convulsions produce reflex spasms of the blood vessels which lead to an increase in blood pressure, and this is followed by apoplexy and hemorrhages in the eyes, kidneys, liver, etc. The same reflex spasms of the blood vessels may be produced by large recurrent placental hemorrhages. When the sodium content of the blood is lowered by means of a water diet and a salt-free diet, eclampsia does not occur. The author looks upon eclampsia not as a poisoning but as a morbid reaction of the body against the normal metabolic products of the ovum under abnormal or unphysiologic modes of living.

J. P. GREENHILL.

Hayes, B. A.: Urinary Back Pressure as a Cause of Toxemia of Pregnancy, Urol. & Cutan. Rev. 40: 545, 1936.

Prior to delivery the author treated 39 patients with pernicious vomiting, preeclamptic toxemia, or eclampsia. All the mothers showed immediate improvement after the kidneys were drained and all ultimately recovered, with some showing more or less permanent kidney damage. Among 19 with pernicious vomiting, only one miscarriage was observed, and that was in a syphilitic mother. Infant mortality is not higher, in fact less by this method of treatment than by more conservative methods, such as rest, sedation, and intravenous glucose.

Based on the findings in this series the logical treatment for such conditions divides itself into two general headings. Preventive treatment can be achieved by seeing to it that at all times throughout pregnancy the urinary tract is open

and drains properly. This merely necessitates proper watchfulness on the part of the obstetrician and the services of a urologist at such times when ordinary measures do not suffice. Curative treatment more or less resolves itself into the treatment of emergencies such as eclampsia, pernicious vomiting or severe nephritic states. Cystoscopic drainage provides the quickest and most certain relief of these conditions and paves the way for any subsequent procedures.

J. P. GREENHILL.

Guthmann, H., and Hildebrandt, H.: Influence of the Sex of the Child on the Origin of Pregnancy Toxicosis, Monatschr. f. Geburtsh. u. Gynäk. **101**: 264, 1936.

In the opinion of the authors, under certain conditions the sex of the child has a definite influence on the development of the toxemias of pregnancy, especially eclampsia. The conditions for this relationship are as follows: (1) The simultaneous occurrence of overfeeding of protein and fat and the presence of a male child; (2) An undernourished individual who has taken an excess amount of protein and fat and has a male child. In women with multiple pregnancies, male children are particularly likely to have an effect on the development of eclampsia and pre-eclampsia. In multiple pregnancy there is a 33 per cent excess of males. Women who have multiple pregnancies are twice as likely to develop the toxemias of pregnancy as those who have single gestations, and they are three times more prone to have eclampsia.

J. P. GREENHILL.

Nordlander, E.: The Relation of the Blood Pressure During Pregnancy With Special Reference to the Connection Between Hypertension and Pregnancy Toxemias, Acta obst. et gynec. Scandinav. **17**: 456, 1937.

Nordlander studied the blood pressures of 3,417 pregnant women. He emphasizes that a high systolic blood pressure at the time of the first prenatal visit has no significance. The more stable diastolic blood pressure is of greater value. The author found that a strict diet had a favorable effect on the toxemias of pregnancy. He observed that an increase in blood pressure occurred as the first symptom in one-fourth of the toxemia cases. He emphasizes that more reliance should be placed on the diastolic blood pressure than has been done previously.

J. P. GREENHILL.

Strauss, Maurice B.: Observations on the Etiology of the Toxemias of Pregnancy, Am. J. M. Sc. **195**: 728, 1938.

Whether there is manifest edema or not, water retention is nevertheless present in greater or less degree in a large proportion of women during the last trimester of pregnancy. It may amount to as much as 10 per cent of body weight. This water retention is primarily conditioned by the level of the plasma proteins. The amount of water retained is in inverse proportion to the osmotic pressure of the plasma proteins. Unless the plasma proteins are below a certain level, a regime consisting of 1,500 c.c. of skimmed milk daily, and hence extremely low in sodium but relatively high in calcium and potassium, will result in the elimination of retained water.

J. THORNWELL WITHERSPOON.

Fan, C. S.: Eye Changes and Residual Hypertension in Toxemia of Pregnancy, Chinese M. J. **53**: 211, 1938.

In the toxemias of pregnancy, studies of the eye grounds furnish valuable information. In a small group of Chinese patients with toxemia of pregnancy 70 per cent exhibited fundus changes. Their relative rate of incidence and severity were closely related to the height of the blood pressure during the toxemia. In

50 per cent of all the toxemic cases the hypertension persisted after termination of the pregnancy, a fact which indicated permanent vascular damage. The rate of incidence of this residual hypertension was found to be related to the height of the blood pressure ante partum and, again, to the rate of incidence and severity of the eye ground changes.

C. O. MALAND.

McIlroy, A. Louise, and Rodway, Helen E.: Weight Changes During and After Pregnancy, With Special Reference to Early Diagnosis of Toxemia, J. Obst. & Gynaec. Brit. Emp. 44: 221, 1937.

The 1,000 patients (primigravidas 704, multiparas 296) were kept under observation from the twenty-fourth week of pregnancy to term. The average periodic gain in weight was in primigravidas 11 pounds 2 ounces, in multiparas 11 pounds 7 ounces. The maximal increase occurred from the twenty-fourth to the twenty-eighth week, 3 pounds 5½ ounces. The minimal increase occurred from the thirty-eighth to the fortieth week, 2 pounds 4 ounces. All the patients showed lower increase in weight than that found by other observers. This was probably due to the advice given to every patient as to dieting and exercise to prevent onset of toxemia.

The age of the patient has an influence on the gain in weight in pregnancy. The older the patient the less increase there is in weight. The least gain occurred in patients of 36 and upward, being two-thirds less as compared with patients of 30 or under. Parity has little or no influence; there was slight average total gain however, in multiparas, 11 pounds 7 ounces, as compared with primigravidas, 11 pounds 3 ounces. Heavy patients showed less gain in weight than those of lighter build.

The weight of the infant seems to have little influence on the changes in maternal weight. The infants of primigravidas were rather heavier if the maternal weight showed much increase. In this series there was little difference in the gain in weight of the patients who gave birth to infants of 10 pounds or more and those of 5 pounds or less.

Decrease in weight occurs during the last two weeks before delivery in a number of cases: 22.5 per cent in primigravidas and 22.15 per cent in multiparas. A few patients showed a periodic loss of weight throughout pregnancy. This is difficult to explain and may be due to tissue loss owing to excessive fetal demands, although these patients did not show marked evidence of malnutrition. Loss of weight is, as a rule, due to increase in exercise, reduction of carbohydrate intake and increased elimination.

In the 75 cases of toxemia, average age was 33. Average periodic gain and total increase of weight were greater in this group. From the twenty-fourth to the thirty-eighth week the gain in weight was 50 per cent greater than in the normal cases. During the last two weeks of pregnancy it was almost three times as much as in the normal cases. Total gain was 1½ times that of the nontoxic cases.

Excessive or rapid gain in weight is in most cases due to errors in diet and lack of regular exercise. Reduction of weight is definite when the carbohydrate intake is lessened and more walking exercise is carried out. Excessive gain may also be due to edema of the tissues, although not evident on clinical examination until later. Some toxic patients, however, had marked edema without excessive gain in weight.

Prevention of toxemia and early recognition of signs of its onset are to be obtained by careful attention directed to the routine weighing of antenatal patients.

Seven hundred and ten patients were weighed approximately six weeks after delivery, and it was found that primigravidas showed an average loss in weight of 21 pounds 5 ounces and multiparas, of 18 pounds 14 ounces. Birth weight of the infant accounted for one third of the decrease in primigravidas and two-fifths in multiparas.

J. P. GREENHILL.

Vignes, H.: Effects Produced by Illumination on Eclamptic Convulsions, Rev. franç. de gynéc. et d'obst. 33: 588, 1938.

Stimulation by light is particularly harmful to women with eclampsia and pre-eclampsia. Hence most authors insist upon placing women with eclampsia in a darkened room. Vignes decided to determine whether light would have any effect on the blood pressure of eclamptic women. He first experimented with men, non-pregnant women, women who were normally pregnant and others. He found that the sudden lighting up of a dark room had no immediate effect on the arterial pressure in half of the cases investigated. In some cases there was a mild elevation and in others a slight decrease in the pressure. However a slight elevation was more constant in pregnant women, and it was constant in women who had toxemia. In this connection the author mentions that Benoit showed that light is a stimulant of the anterior pituitary especially the part which is concerned with the gonadotropic function. This effect is absent if the optic nerve is cut or the eyes are removed. There is also an effect on the pars intermedia, and there may be an effect on the posterior hypophysis. Because of this, Vignes warns against sudden illumination in cases of eclampsia.

J. P. GREENHILL.

Von Bud, G.: Pregnancy Toxicoses and Tumors: New Points of View on Etiology of Tumors, Arch. f. Gynäk. 163: 439, 1937.

Bud maintains that the pregnancy toxicoses are caused by focal toxins, the therapeutic results he obtained with the extirpation of foci corroborate this. In a previous paper on convulsive eclampsia he had called attention to the effects of focal toxins on the nervous system. Moreover, on the basis of his studies on eclampsia without convulsions, on ileus and pyelitis and on the basis of clinical observations, he believes that the cause of puerperal fever is to be found in a disturbance of the nervous system, which in turn is elicited by focal toxins. On this basis could be explained also diseases of the ovum and placenta and the congenital predisposition to disease. Malignant and benign tumors which developed after some conditions of irritation of the nervous system (eclampsia) and after paralytic-atonic pregnancy toxicoses (ileus and pyelitis), directed the author's attention to the fact that the focal toxins not only exert an irritating effect on the nervous system but may lead also to tumor formation by way of trophic disturbances.

J. P. GREENHILL.

Keller, Arnott and Mathews: Observations on Morbid Histology of the Kidney in Eclampsia and Other Toxaemias of Pregnancy, J. Obst. & Gynaec. Brit. Emp. 44: 320, 1937.

These writers selected a unique series of over 70 cases of women dying of eclampsia, pre-eclampsia, hyperemesis, cortical necrosis, and accidental hemorrhage.

On the basis of their study of the acute lesion, the authors believe that it is not unreasonable to suppose that in a certain number of cases the lesion will progress and develop into fully established chronic nephritis. Whether or not the lesion can remain stationary and form a type of occult or subliminal nephritis, causing trouble only under the stress of a future pregnancy, it is impossible to say.

J. P. GREENHILL.

Zimmerman, H. M., and Peters, J. P.: Pathology of Pregnancy Toxemias, J. Clin. Investigation 16: 397, 1937.

Case histories and necropsy findings on 23 patients who died as a result of the direct or remote effects of pregnancy toxemias are reported. Although characteristic tubular and glomerular lesions were usually found in the kidneys of patients who died in the acute stages of toxemias with eclamptic syndromes, these lesions, like hepatic necroses, were not found exclusively in eclampsia.

Eclampsia could not be distinguished from other toxemias on the basis of either pathogenesis or morbid anatomy. Lesions of "malignant nephrosclerosis" were encountered frequently. Both acute nephritis of infectious origin and antecedent vascular disease apparently gave rise to toxemias, which sometimes had eclamptic manifestations. A great variety of vascular or renal diseases may act as predisposing causes for toxemias; pregnancy appears to give them a distinctive coloration and an explosive character.

J. P. GREENHILL.

Weinberg, Arthur: Various Manifestations of Late Toxemia Occurring in Successive Pregnancies, Virginia M. Monthly 65: 290, 1938.

The author presents the history of a woman who eighteen years previously, with her first pregnancy, had developed eclampsia and was delivered of a stillborn infant. Her second and third pregnancies were normal. During her fourth pregnancy a diagnosis of low reserve kidney was made, but the pregnancy was terminated successfully at term. During her fifth pregnancy a diagnosis of chronic nephritis was made. Again pregnancy terminated successfully. Her sixth pregnancy passed the same as her fifth. Two years prior to the present or seventh pregnancy, while in a nonpregnant state, a diagnosis of chronic glomerulonephritis was made and the patient was placed on a proper diet. During the present pregnancy the patient had had no prenatal care and was admitted to the hospital as an emergency three weeks before term because of a fulminating late toxemia of pregnancy. She was treated conservatively, but died forty-six hours after admission to the hospital. Autopsy revealed not only a chronic glomerulonephritis, but also the hemorrhagic periportal necrosis of a recent eclampsia. The case is of interest because it shows that eclampsia may give origin to chronic nephritis; that eclampsia may recur at subsequent pregnancies; that the ultimate fate of repeated pregnancies in the face of toxemia is death to the patient; that eclampsia and chronic nephritis can resemble each other, and that they may exist concurrently.

EUGENE S. AUER.

Black, James: The Treatment and Prognosis of the Toxaemias of Pregnancy With Special Reference to Future Pregnancies, South African M. J. 12: 88, 1938.

Observing the blood pressure, noting the presence of edema, and testing the urine for albumin will make early diagnosis of eclampsia possible in nearly every case. By doing this, the author feels, 80 to 90 per cent of the cases can be prevented. In his experience, blood pressure elevation is usually the first and albuminuria the last symptom to appear.

He warns of carrying eclamptics to viability of the fetus only to get permanent kidney damage in the mother. When he deems interruption advisable, cesarean section is usually not even considered. The toxemias of pregnancy leave permanent kidney damage in from 10 to 25 per cent. A wait of at least a year is advised before a subsequent pregnancy is begun and then only after careful examination shows a normal cardiovascular renal system. If the examination reveals polyuria, slight albumin, a specific gravity always below 1012, and a systolic blood pressure of 140 or more, proof of permanent damage is present. These cases are emphatically advised against pregnancy.

In the intermediary group, it is much harder to advise. Here more detailed tests, as blood urea, uric acid determinations, and urea concentration tests, may prove of value.

F. L. ADAIR AND JOHN A. HAUGEN.

McCord, J. R.: Conservative Treatment of Eclampsia: Study of 148 Cases, J. M. Soc. New Jersey 34: 9, 1937.

McCord thinks that a mortality rate of 6.75 per cent in 148 consecutive cases of eclampsia is low and that certain information which has been obtained merits discussion.

Prenatal care should mean meticulous and frequent supervision, but even so prevention of eclampsia is not always possible. The fact that 95.83 per cent of the author's patients had hypertension before they had convulsions emphasizes the great value of watching the blood pressure.

Some method for the induction of labor was used in 48.61 per cent of the cases.

Conservative therapy, namely, morphine, magnesium sulfate and intravenous dextrose, will usually control convulsions, coma and shock. In most instances, labor should not be induced until conservative measures have failed.

Delivery was spontaneous in 86.01 per cent of the cases.

In this series, 76.54 per cent of the babies were living when discharged from the hospital. However, 24.13 per cent of these were prematures, and it is probable that the later mortality in this group was high.

The danger of chronic hypertensive and renal diseases following pregnancy toxemias is real and is always to be considered in any expectant plan of treatment for pre-eclampsia. McCord does not believe that the expectant plan is ever justified in severe pre-eclampsia. Labor should be induced promptly and the woman allowed to deliver in a safe, sane, and conservative manner. Duration of the pregnancy should not influence this decision. Routine examination of eye-grounds yields valuable information for proper evaluation of the toxemia.

J. P. GREENHILL.

Stroganoff and Davidovitch: Early Artificial Rupture of Membranes in Prophylactic Treatment of Eclampsia, Gynéc. et obst. 35: 220, 1937.

The authors discuss the value of early artificial rupture of the membranes in cases of eclampsia, reserving the term "early artificial rupture" for cases in which the os is less than 5 cm. in diameter.

They have so treated 179 patients; 35 were not in labor, and on an average delivery occurred twenty-five hours later. In seven of these patients labor was prolonged: in four it lasted 44 hours, in two 50 hours, in one 108 hours.

Eighty-two patients (46 per cent) had no further seizures after the membranes were ruptured. Excluding 16 cases of post-partum eclampsia, the average number of fits in each case was 2.3. The average for 91 later cases was only 1.9. In view of the fact that the procedure was reserved for severe cases, the maternal mortality was relatively high, 17 deaths in 179 cases (9.5 per cent). In the last 81 cases there were five deaths. Fetal mortality was 27 per cent.

J. P. GREENHILL.

Stroganoff, W., and Davidovitch, O.: Two Hundred Cases of Eclampsia Treated With Magnesium Sulfate: Preliminary Report, J. Obst. & Gynaec. Brit. Emp. 44: 289, 1937.

In summarizing their investigation and observations, the authors state that magnesium sulfate is a powerful means of fighting eclampsia and that it seems highly probable that they shall succeed in reaching the ideal they aimed at, namely, to reduce mortality in eclampsia below 0.5 per cent for patients who are not far advanced and in whom severe complications are absent, and to 2.5 to 4 per cent in cases showing such conditions.

Certain drawbacks connected with administration of magnesium sulfate should, however, be noted. (1) In some cases, though rarely, the remedy causes threatening symptoms of poisoning, which may even lead to fatal issue if an antidote is not administered. (2) The abscesses which may occur on the site of the injection and which delay recovery for weeks, sometimes cause other unpleasant complications. (3) Both their own observations and literary data seem to indicate that the nervous system is more severely affected by this drug than by chloral hydrate. The authors had 2 per cent of psychoses among patients of this group and only 1 per cent among those treated with chloral hydrate. (4) The authors were surprised to observe so high a mortality among women having a multiple pregnancy (four fatal issues in 10 cases). Whether this was accidental or is a regular

phenomenon will be seen from further observations. (5) The number of hemorrhages observed was high, i.e., eight of the 29 cases of eclampsia which developed during pregnancy or labor.

The authors note with satisfaction that cesarean section, an operation which deforms a normally built woman and threatens her with severe consequences, is scarcely ever used as a means of fighting eclampsia. They have conducted the treatment of over 1,000 cases of eclampsia without resorting to it.

J. P. GREENHILL.

Emmrich, J.: Short Wave Therapy in the Treatment of Preeclampsia and Eclampsia, Zentralbl. f. Gynäk. 61: 1165, 1937.

Twenty-four patients with eclampsia and pre-eclampsia were treated by short wave therapy. The treatments were applied to the kidneys, and also to the head if there were cerebral symptoms such as convulsions, fainting, headache and visual disturbances. The favorable results obtained, in his opinion, are due to a resulting active hyperemia especially in the kidneys. This therapy exerts a favorable action on vascular spasms.

J. P. GREENHILL.

Robson, J. M., and Paterson, S. J.: Progesterone in Pre-Eclamptic Toxaemia, Brit. M. J. 1: 311, 1937.

Certain experiments, in which toxic conditions leading to death were produced in pregnant rabbits, are described; these conditions were associated with a failure in the secretion of the luteal hormone.

The results obtained following the administration of progesterone in twelve patients suffering from severe pre-eclamptic symptoms are given. Clinical improvement appears to have been produced in these cases.

It is evident that the numbers are too small to establish formal proof of the efficacy of the treatment, and the results are published at this stage because it would take many years to collect adequate data in a single hospital. The results appear to be sufficiently encouraging to deserve testing on a wider scale without delay.

F. L. ADAIR AND S. A. PEARL.

Yasunami, H.: Clinical Application of Vitamin B, Especially Vitamin B_1, for Toxemia Gravidarum, Jap. J. Obst. & Gynec. 21: 239, 1938.

The author administered vitamin B to women who had hyperemesis gravidarum, nephropathy gravidarum, pre-eclampsia, and eclampsia. No other treatment was given and the patients rapidly recovered. The treatment was most effective in the cases of pre-eclampsia because in them it prevented the occurrence of convulsions. There were no complications following this therapy.

The author observed that his patients with toxemia usually came from the class of women whose standard of living was low. These women had an insufficiency of vitamin B. The author believes that the administration of vitamin B during pregnancy will prevent the toxemias of pregnancy.

J. P. GREENHILL.

Falls, F. H.: Management of Eclamptogenic Toxemia, Northwest Med. 36: 1, 1937.

In the opinion of the writer eclamptogenic toxemia can be controlled in most cases by reducing the amount of protein-split products in the blood and increasing elimination by the bowel. When symptoms do not yield to conservative management, the uterus must be emptied. Cesarean section is indicated in patients with fulminating toxemia or in any patient when induction of labor or delivery from below is contraindicated.

Eye ground examination is of little value as an aid in determining the severity of a given case, but the phenolsulfonphthalein test is of value prognostically.

Treatment should be continued post partum until the symptoms have definitely improved in order to reduce the incidence and severity of post-partum convulsions. Sedatives, intravenous magnesium sulfate injections and intravenous glucose injections, while rational and in some cases helpful, are not essential as part of ante-partum treatment. Patients first seen in labor are usually best delivered from below. Elderly primiparas near term but not in labor are best delivered by cesarean section because of the danger and uncertainty of delivery by induction of labor.

There is no advantage in dividing these cases into eclampsia, low reserve kidney, pre-eclampsia, and eclampsism. Because of the prematurity and toxic condition of the babies in these cases, extra precautions must be taken to insure their safety during labor and in the first days thereafter.

J. P. GREENHILL.

Correspondence

Anovulatory Menstruation

To the Editor:

In the article on "The Incidence of Anovulatory Menstruation Among Patients of Low Fertility" which appeared in the January issue of your journal, Drs. Rock, Bartlett and Matson stress the difference in the incidence of the condition in their reported group of cases as compared with those reported by Drs. Mazer, Israel and Kacher in *Surg. Gynec. Obst.* 65: 30, 1937.

May I call attention to the fact that the discrepancy is the result of a difference in the selection of cases. The incidence of anovular menstruation in 9.1 per cent reported by them is based on a study of 392 sterile women with a multiplicity of causative factors; whereas the incidence of 30 per cent of anovular menstruation reported by us is based on a study of 65 sterile women, selected from a much larger group, because in them there was no accountable cause for the existing sterility.

We definitely stated in the publication that the study was made on sterile women in whom there was no accountable organic cause for the sterility and whose mates were found to be fertile. This is indeed a restricted group as compared with the all-inclusive type of patient studied by Drs. Rock, Bartlett, and Matson.

CHARLES MAZER, M.D.

Philadelphia, Pa.
January 27, 1939

To the Editor:

In reply to Dr. Mazer's letter, I consider his point is well taken, as our respective figures are not exactly comparable. Perhaps mistakenly we thought it unnecessary to extend the discussion, for even if we omitted from the two groups of ovulating and of anovulating women all those whose infertility could be attributed to some other disturbance, we found that among the remainder our incidence of anovulatory menstruation, as we defined it, and according to our indices of progestin effect in the endometrium, was not materially changed, and was much lower than their figure. I suspect from the photomicrographs accompanying Dr. Mazer's paper that the discrepancy is at least partly due to differences in cytologic criteria of progestational endometrium.

JOHN ROCK, M.D.

Boston, Mass.
February 15, 1939

To the Editor:

Your recent editorial on "The Dosage of the Estrogens" which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY; 36: September, 1938, as well as the comments by Dr. Curtis in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY; 37: January, 1939, were of the keenest interest to me because they concern the confusion unfortunately existing in this field.

In this connection may I draw your attention to some statements in the recent letter to the editor mentioned above. In the third paragraph it is stated that "Two international units of estrogenic materials have been established, one for estrone, the other for estradiol." In this sentence "estradiol" should be replaced by "estradiol benzoate," as the later international benzoate unit was established for this substance.

Furthermore, the classification of different preparations given in the fourth paragraph should rather list menformon among the preparations containing estrone (ketohydroxyestrin), while progynon DH, as well as dimenformon, contains estradiol and progynon B, like dimenformon benzoate, contains estradiol benzoate.

I hope this will help to clarify the situation.

B. L. JOSEPHY, M.D.
Scientific Director, Roche-Organon, Inc.

Feb. 1, 1939.

Books Received

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DIE HYPERTONIE DES INNEREN BLASENSPHINKTERS. By Professor Dr. Hans Rubritius in Wien. 22 Seiten. Verlag von Georg Thieme, Leipzig, 1938.

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American Journal of Obstetrics and Gynecology

VOL. 37 JUNE, 1939 No. 6

Original Communications

PITUITARY GONADOTROPIC EXTRACTS FOR TREATMENT OF AMENORRHEA, MENORRHAGIA, AND STERILITY*

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MADISON, WIS.

(From the Departments of Obstetrics and Gynecology, and Medicine, University of Wisconsin)

IN A number of the disorders of menstrual rhythm and of fertility, endocrine deficiencies are assumed to be major factors. Numerous reports have appeared in the past decade to illustrate the types of tissue reactions found in the uterus, vagina, and ovaries with experimentally produced endocrine disturbances in animals. Attempts to build diagnostic differentiations on this foundation have made progress, as we have indicated in a previous paper.[1] It is increasingly our impression that the endocrine responsibility for amenorrhea, oligomenorrhea, menorrhagia, irregular cycles, and sterility with anovulatory bleeding is to be considered pituitary hypofunction. The various clinical pictures mentioned are due to variations in quantity of gonadotropic hormones liberated and to abnormalities in the timing of this secretion which determines the cyclic activity of the ovaries. One way to prove such a thesis would be by quantitative assay of blood from patients, as compared with normally fertile and regular women. This method has been attempted by competent investigators, but suffers from such difficulties as a lack of information about normal cycles, debate as to the significance of certain

*These studies have been aided by a series of grants from the Wisconsin Alumni Research Foundation.

It was the pleasure and good fortune of the authors to have the participation of Dr. F. L. Hisaw in the earlier years of the studies here reported. We gladly record our gratitude for the assistance of Drs. Wm. E. Bayley and J. Stewart in tissue study, of Mrs. June Golden in vaginal epithelial study, and Miss Linda Arneson, whose dependable preparation of tissues has contributed to our confidence in the comparison of biopsy specimens.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

types of assay technique, and the expense of extended assays of specimens throughout one or more cycles. Endometrial biopsies at selected times in the cycle help to avoid some of these problems. They fall short of giving quantitative measures of the amount of ovarian hormones acting, and therefore of the amount of gonadotropic hormones available. The use of the vaginal smear study of Papanicolaou and Shorr[2] has enabled us to proceed further in the direction of time and intensity analysis of the disturbances mentioned above. The manner in which these methods are combined will be illustrated by case studies. We present at this time cases selected to show several types in which success or failure has attended the therapy prescribed after diagnostic studies had been made. The therapeutic results contribute further evidence to validate the diagnostic grouping. The cases presented have been under observation long enough to warrant certain deductions even though they are no more striking than other cases studied for shorter periods of time, but with similar results. Treatment may not achieve desired results because of many reasons ranging from inaccurate diagnosis through inadequate cooperation to inability to simulate even roughly the natural rate of secretion of gonadotropic materials by the intact anterior pituitary gland.

The therapy has been based on the hypodermic administration of aqueous extracts of the anterior lobe of standardized potency. Our most extensive experience is with the use of the extract as originally prepared by our former colleagues, Hisaw and Fevold,[3] marketed by Chappel Bros. Laboratory under the name of "Prephysin." More recently we have used "gonadotropic antuitrin," a Parke-Davis preparation made from hog pituitary and supplied to us through the courtesy of Dr. E. A. Sharpe. Still more recently we have used "Gonadogen," a pregnant mare's serum preparation, furnished us by Dr. G. Cartland of the Upjohn Laboratory. We are greatly indebted to the three laboratories for the generous supplies of these materials for this clinical study. The potency of the extracts has been checked for us at times by Drs. F. L. Hisaw and R. K. Meyer in the Department of Zoology. The only difficulties attending the use of the extracts has been a variable local reaction at the site of injection in many cases. Rarely has this interrupted the plan of treatment. In two cases urticarial reactions demonstrated allergic sensitization which necessitated discontinuance of injection. No allergic reactions have occurred *after* the first series of injections, a fact which surprised us since the extracts are known to contain small amounts of protein. The doses employed have been 1.0 c.c. daily or on alternate days, as indicated in the charts. These doses contained from 5 to 100 "units" each, although the definition of the unit is only roughly similar for the three preparations referred to above.

The timing of the therapy is considered of especial importance. As our concepts of the time of increasing activity in the pituitary, the ovaries, and the endometrium have developed, we have been convinced that the sharp increase in the secretory action of the follicle occurs at about the onset of a menstrual flow. We have therefore adopted the

onset of flow as the optimal time at which to begin use of a gonadotropic factor when follicle stimulation was the objective. Since there is increasing certainty that in a fertile twenty-eight-day cycle ovulation occurs on about the fourteenth day, we have attempted to concentrate the therapy in the first fourteen days. The reason for our insistence on not using continuous injections of a potent gonadotropic substance is that such treatment has produced follicle cysts in animals and may conceivably do so in the human being. It is our belief that long continued (and possibly low intensity) pituitary stimulation is the background of many cases of polycystic ovaries. With this caution in mind we have been alert to the possibility of producing cysts by our program, but to date have been unable to detect such a result. Judging from results with monkeys it should be possible to induce ovulation in a matured follicle by the intravenous injection of a mixture of the two anterior pituitary hormones.[4] We have made numerous attempts to do this but our success has not been dependable enough to present. This we attribute to the difficulty in securing a regular supply of extract which is high in its content of the "luteinizing hormone." Therefore we have confined our attempts to the use of mixed follicle stimulating and luteinizing materials hypodermically, in interrupted series beginning with the onset of each flow. When there have been long periods of amenorrhea, we have resumed therapy usually after thirty-two days from the last preceding flow or the last preceding series of injections. This plan was devised to coordinate the injected pituitary materials with those secreted by the patient's gland during the same cycle. It is possible that ultimately we may come to an even more physiologic plan of treatment with continuous daily therapy, varying the doses when we have better evidence bearing on the rate of activity of the normal gland. At present we prefer to remain on the side of undertreating the patient, even though we may have failures when larger doses might have produced greater success.

SECONDARY AMENORRHEA

E. M., unmarried, 23-year-old white woman, was referred because of obesity, variable edema, and amenorrhea. Menarche occurred at 13 years of age, cycles were of four-weeks' type with one week of flow, but infrequent menses and obesity appeared and amenorrhea of two years preceded the study. Symptoms included irritability, hot flashes, palpitation, dyspnea, vertigo, morbid melancholy and worrying, and paresthesias. Basal metabolic rate +20 per cent and blood pressure 130/80. Pelvic examination showed a definitely small uterus but no other findings. Endometrial biopsy procured tissue without evidence of any activity, i.e., essentially as in a castrate (Fig. 1, *a*). The only therapy used was the 1,200 calorie reduction diet and "prephysin" given in series of 7 to 10 daily doses of 25 units each, at 4-week intervals. Two "menstrual" flows occurred, but a second biopsy taken four weeks after the fourth series of injections was begun showed no more active tissues than before therapy. The treatment was increased to 15 doses in each series, and after 8 such series flows of five to seven days each began to occur at intervals between four and six weeks. Dietary cooperation was almost nil for the first year, but improved when the patient began to see results of the injections. After 21 series of injections, in twenty-two months, during which 13 flows had occurred, the patient was allowed to go through a cycle without therapy, and on the twenty-fourth day another biopsy was obtained. This proved to have a follicular type of activity about as might be expected in the second week of a normal cycle, although not too well developed. The

result was considered indicative of progress. The details of injection were altered to accord with the routine advised above, i.e., each series was begun when and only when a flow appeared, instead of at arbitrary four-week intervals.

Regularity of menstrual rhythm continued its improvement toward a four-weeks' type. A fourth biopsy, taken late in the fourth week after 5 more cycles of treatment, showed no changes, however (Fig. 1, *b*). It was concluded that further therapy required still greater intensity of pituitary stimulation, plus probably intravenous

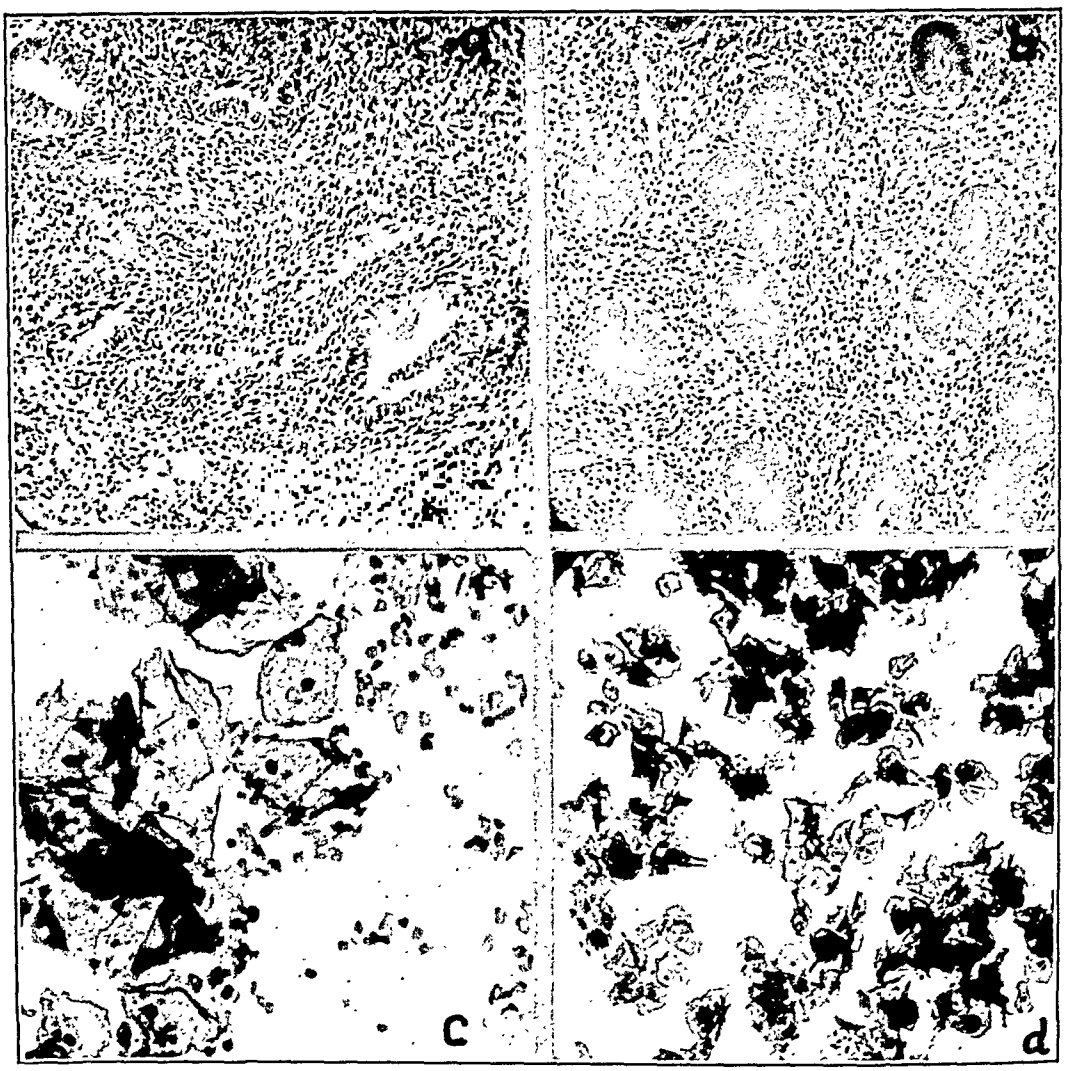


Fig. 1.—Case E. M. (*a*) First biopsy, showing "castrate" inactivity. (*b*) Fourth biopsy, on twenty-fifth day of cycle under treatment, showing only estrin activity. (*c*) Vaginal smear on ninth day of same cycle with (*b*), showing some cornified cells and many small cells from deep layers. (*d*) Vaginal smear on 16th day of a cycle when 15 daily doses of 100 units each of prephysin were given, showing increased clarity, with some cornified cells.

administration of the material to secure ovulation. The number of daily injections was increased to 15, and next the anterior pituitary material used was changed to doses with 100 units per c.c., 4 times the potency previously employed. As a method for studying the activity of the ovaries in response to this stimulation, vaginal epithelium was examined by the Papanicolaou and Shorr technique. Samples taken on the fourteenth to sixteenth days of several cycles showed obvious estrogenic hormone activity (Fig. 1, *c* and *d*), but this was below the intensity associated with the end of the normal second week.

The partial results accomplished in this woman, after thirty-four months during which the cycles of therapy have been interrupted only twice, demonstrate that large doses of gonadotropic material will probably be required for the treatment of even secondary amenorrhea. There has been clinical improvement, shown by menses occurring every four to six weeks for two years, with rare shorter intervals, by mammary development, by improved secondary sex characters, and by improved interest in weight control as a consequence of which she has followed diet limitations and reduced by 27 pounds during the interval. It is debatable whether the results justify the costs. The patient and referring physician continue to feel that they do.

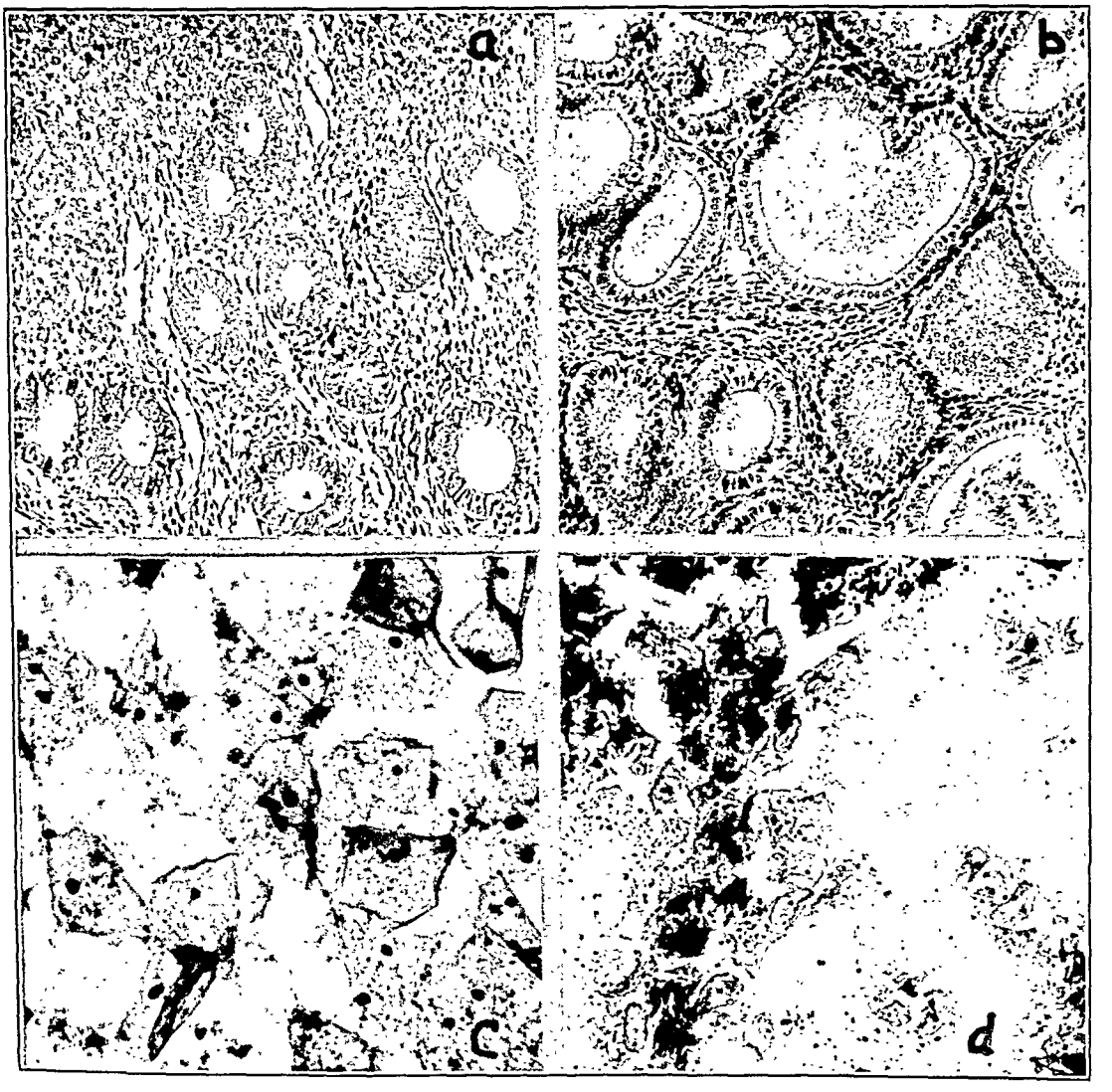


Fig. 2.—Case El. Mo. (*a*) Biopsy on twenty-seventh day of thirty-three-day cycle, showing low intensity of estrin action. (*b*) Biopsy on thirty-first day of thirty-four-day cycle showing some evidence of progestin action. (*c*) Vaginal smear on fourteenth day of a cycle without therapy, showing a few cornified cells, but not typically clear specimen of full estrin activity. (*d*) Vaginal smear of twenty-seventh day of same cycle (proved anovulatory), simulating premenstrual picture.

E. M., unmarried, twenty-two-year-old white woman, referred because of obesity, amenorrhea, and lack of secondary sex characters, had not flowed for thirteen months. Menarche occurred at sixteen years of age; the cycle was always irregular, infrequent, and with brief flows. There were no nervous symptoms. Basal metabolism had been brought up to normal range by use of thyroid and was continued so throughout the entire period of study, but without effect other than that, combined with the 1,200 calorie diet, weight was brought down to optimal levels. Pelvic examination showed nothing unusual. During the first year estrogenic material was used, but with no

subjective changes and no flow. Then for six months pregnancy urine concentrate was given without help. Then there followed seven months with combined pregnancy urine and "prephysin," during which interval 5 flows appeared. For the following year the patient took only thyroid, and recorded 9 flows in twelve months. Following this came a period of thirty months' use of "prephysin," in series of 5 doses of 25 units each, repeated 25 times, with obvious improvement in secondary characteristics (leading to engagement to be married), and the occurrence of four- to five-week cycles, with three- to six-day flows. The "prephysin" was then omitted for 8 cycles, following which there was a tendency to longer cycles, less copious flow, and the patient returned to the therapy with return of more normal type of flow. Biopsy was not obtained at the start of the study, but on two occasions during the treatment it was secured. The earlier of these (Fig. 2, *a*), in the late fourth week of a thirty-three-day cycle after 9 series of injections showed only low grade follicular action, but seven months later on the thirty-first day of a thirty-four-day cycle, a good progestational endometrium was demonstrated (Fig. 2, *b*). After 11 cycles of therapy in the course of twelve months, the pituitary injections were interrupted for a single month. On the fourteenth day of the cycle a vaginal epithelial sample showed moderate development of estrogenic stimulation. This subsided during the next two weeks as expected. Determination of pregnandiol excretion in twenty-four-hour urine samples during the fourth week showed that a corpus luteum did not form, i.e. there was no pregnandiol excretion. This confirms Papanicolaou and Shorr's report[2] that the "premenstrual" vaginal smear cannot be accepted as evidence of progestin action.

This patient has made definite gain under combined therapy. The use of thyroid cannot be considered the chief cause of the improvement, for it was used throughout. Ovarian activity is complete at times in that the estrogenic and progestational hormones are being formed, although the intensity and regularity are such that probably fertility is not yet possible. It is considered that further treatment with increased doses of pituitary material is justified and necessary if results are to be optimal.

Z. R., an unmarried woman of 24 years, had been under medical care for irregular and infrequent menses since age of 19. Menarche at 15 had been followed by flows at intervals of six weeks to three months, duration four to five days, without other unusual findings. There was a slight tendency to obesity. The lowest basal metabolic test recorded was 23 per cent below the expected level. Thyroid therapy was begun at the age of 19, and continued, with determinations of basal rate, to maintain the patient at the normal level. This led to no improvement in the menstrual rhythm. Pelvic examination at age of 24 showed a distinctly small uterus, with small ovaries. The breasts were rather small. An endometrial biopsy was obtained on the forty-first day after a flow appeared, and showed a very low intensity of estrogenic hormone stimulation. This was followed at once by a three-day flow. (Biopsy technique never produces this result in normal types of cycle.) The treatment with pituitary extract was begun, using 10 doses of 25 units each in fifteen days, repeated each four weeks. After 5 series of doses the progress was not evident, and the dose was changed to 100 units at each injection. Vaginal epithelium examined during the second week of such series of injections failed to show more than a trace of estrogenic hormone influence in spite of fifteen consecutive days' therapy. The material used was changed to gonadogen (Upjohn). After the use of 15 daily doses of 10 units each, and also of 15 daily doses of 20 units each, the estrogenic activity was no more intense than it had been previously.

As a consequence of this period of intensive stimulation, with varying doses of two types of gonadotropic material, but with little evidence of improvement in ovarian performance, this patient has been advised to abandon treatment. The prospect is of continued irregularity and sterility. The clinical impression is that the ovaries have for some unknown reason a very limited capacity to respond to stimulation by the pituitary. Aside from the details given there are no evidences of a lack of feminization, or other health problem.

The varying responsiveness to pituitary stimulation shown by these cases is typical of that seen in a large group of patients with complaints of infrequent menses and periods of amenorrhea. The use of the biopsy of endometrium and the vaginal epithelium readings obtained with a pipetted sample enable the clinician to determine in a relatively short period of time whether progress is being made. If estrogenic hormone effects do not become increasingly intense under pituitary stimulation in such patients it seems wise to increase the dosage, and if that fails, to abandon treatment.

MENORRHAGIA

Although the occurrence of excessively long menstrual flow seems diametrically opposite to the amenorrheic state, there is a growing appreciation of the similarity between menorrhagia and amenorrhea in the endocrine activity involved. Although not all cases of prolonged flow are due to absence of progestin action, there are more menorrhagic women with flow from a poorly developed estrin endometrium than with any other type. This statement obviously excludes cases with neoplasm, sepsis, or pregnancy as factors in the flowing. Although our study of deficiencies in prothrombin time show that a few cases of menorrhagia are quickly relieved by the administration of vitamin K, this is probably an infrequent cause of bleeding from the uterus. A few examples of successful treatment of irregular and prolonged bleeding will demonstrate how we have applied methods similar to those described above for amenorrhea.

E. D. was examined at age of 17 because of irregular menstrual cycles at intervals of three to six weeks, with flow varying from two to sixteen days. This condition had been noted since the menarche at 13. Other findings included marked acne, some hot flushes, sweating spells, dyspneic attacks, and paresthesias. Secondary sex characters were not well developed. The basal metabolism was within normal limits. The physical examination including pelvic examination under an anesthetic was not remarkable except for small breasts. Endometrium obtained during a prolonged period of flow showed essentially normal estrogenic stimulation of the tissue, from which bleeding continued (Fig. 3). Since it was evident that the flow was anovulatory, attempts were made to initiate corpus luteum formation by the intravenous injection of 25 unit doses of prephysin. This is known to contain both the follicle stimulating and luteinizing activity of the anterior pituitary. This treatment was given between the eleventh and fourteenth days of three cycles, with results which were encouraging. The systemic and immediate reactions to the introduction of the extract intravenously caused such marked chill and fever, with nausea, that it was considered unwise to persist. The patient was not available for endometrial biopsy to determine whether a corpus luteum was formed at the time of this therapy. It was therefore determined to use the prephysin hypodermically as before described. After this had been done for 17 cycles in the next sixteen months, without any recurrence of menorrhagia, a biopsy was obtained in the early part of the third week without treatment in that cycle. This showed progestational effects within the limits of normal for the time (Fig. 3). The next flow followed five days later. This early flow and the characteristic cycle of twenty-one to twenty-four days which had developed during the treatment led to the belief that the intensity of progestin action was subnormal. After 5 more cycles with similar treatment the patient preferred to omit therapy and see how well the gain could be maintained. There was no essential difference in the next 10 cycles, but during the fifth cycle without treatment, twenty-four-hour urine samples were examined for pregnandiol. The total excretion

during seven days was only 12.2 mg., far below the accepted normal level. It is considered that this woman now has an intensity of pituitary and ovarian activity which is below normal. Since menorrhagia is no longer occurring, and since secondary sex characters have developed satisfactorily, she prefers to omit treatment. In thirteen months without therapy she has had 17 flows, intervals three to five weeks, duration three to nine days, typically four to five days.



Fig. 3.—Case. E. D. (*a*) First biopsy, during third week of menorrhagia; irregular glands, with estrin action. (*b*) Biopsy on sixteenth day of twenty-one-day cycle, showing early effects of progestin.

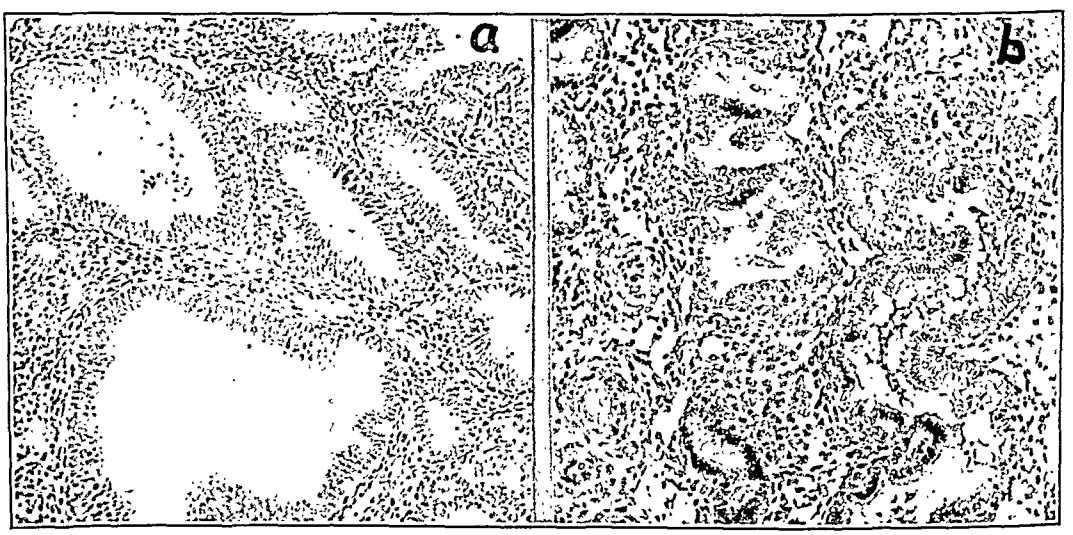


Fig. 4.—Case K. M. (*a*) Curette specimen during menorrhagia, showing the "Swiss cheese" picture, resulting from sustained estrin action. (*b*) Biopsy in fourth week, after therapy, showing evidences of progestin action.

K. M. was referred at the age of 29 because of menorrhagia during flows which lasted three to four days. Anemia was not significant. Menses had been occurring at intervals of three to four weeks. There were occasional flows of two weeks' duration. Mumps had occurred preceding these symptoms at age of 28, but without recognized oophoritis. Other complaints included acne, asthenia without hypotension, nervous irritability, palpitation, headaches, insomnia, morbid melancholy and worrying. The basal metabolism was repeatedly found to be 23 to 30 per cent above the normal, but the clinical picture was not typical of thyrotoxicosis. Pelvic examina-

tion revealed an enlarged and retroverted uterus, which was replaced and supported by a pessary. Curettage done during a prolonged flow removed tissue with areas of glandular and cystic hyperplasia, resembling the "Swiss cheese" type (Fig. 4, *a*). The menorrhagia recurred in the second cycle after the curettage, and therefore treatment was initiated with anterior pituitary extract. The product employed was gonadotropic antuitrin (Parke-Davis and Co.). This material contained 5 to 10 units per c.c.; doses of 1 c.c. were given in similar routines to that used for prephysin. Local reactions were very slight. Improvement was evident after a few months. In the fourth week of a cycle without treatment, endometrium obtained with a biopsy punch showed typical effects of progestin (Fig. 4, *b*), and the flow began on the following day. It was evident that the ovary was forming a corpus luteum. Treatment was resumed for 6 cycles, which varied from five to six weeks in length. Although the duration of flow was still sometimes long, it was not excessively heavy. The patient was feeling well, and preferred to try an observation period without therapy. This was successful, for the next 5 flows, at least, were of ordinary duration.



Fig. 5.—Case B. H. (*a*) Curette specimen during menorrhagia, showing low intensity of estrin action. (*b*) Biopsy in fourth week, after therapy, showing full effect of progestin.

B. H. was referred at age of 17 because of irregular and excessive flows of five days to three months, intervals being highly variable since the menarche at 15. There were also nervous irritability, headaches, tendency to weeping, and breast pains. The basal metabolism was 6 per cent below the standard. Pelvic examination revealed a small and retroverted uterus, which was held up by a pessary, for the following four months. The right ovary was enlarged and cystic. Curettage on the nineteenth day of a flow served to stop the flowing. The tissue obtained showed a low intensity of estrogenic hormone stimulation of endometrium (Fig. 5, *a*). When, therefore, menorrhagia recurred a few months later after two long periods of amenorrhea, it was concluded that the therapy indicated was stimulation of underactive ovaries. The use of 5 doses of 25 units each of prephysin during each cycle for the next year was followed by essentially regular four-week cycles with moderate flow. Treatment was suspended, and endometrial biopsy showed a well-developed progestin effect on the twenty-second day of a twenty-six-day cycle (Fig. 5, *b*). For 10 cycles without therapy menses continued satisfactorily regular, to be followed by longer cycles and recurrence of menorrhagia. It was therefore deemed wise to return at once to the type of therapy which had succeeded in the previous year. Symptoms, which had been relieved, were not severe. Pelvic examination at this time showed that the cystic ovary was no longer palpably enlarged.

Consideration of these three cases of menorrhagia, with checking of excessive flow, improvement in rhythm, and evidence of the formation

of a corpus luteum after treatment, makes it evident that gonadotropic pituitary materials applied to the human being may be the cause of complete ovulatory cycles, and improvement in ovarian function. The necessity for indefinite continuation of such treatment cannot yet be settled. Results to date make it appear that sustained treatment will be found necessary, as might be expected, since this is substitutional pituitary therapy, without reason to expect a cure. In two of the most successful cases mentioned, as in others, we have found "antihormones" present in the blood after treatment had been carried on for some months, but the clinical progress was apparently not impeded, nor were anaphylactic phenomena observed with continued use of the pituitary extracts.[5]

STERILITY

Obviously the most complete test of pituitary and ovarian function is fertility. Of the women who were treated primarily for relief of sterility three are illustrative of the problems to be met.

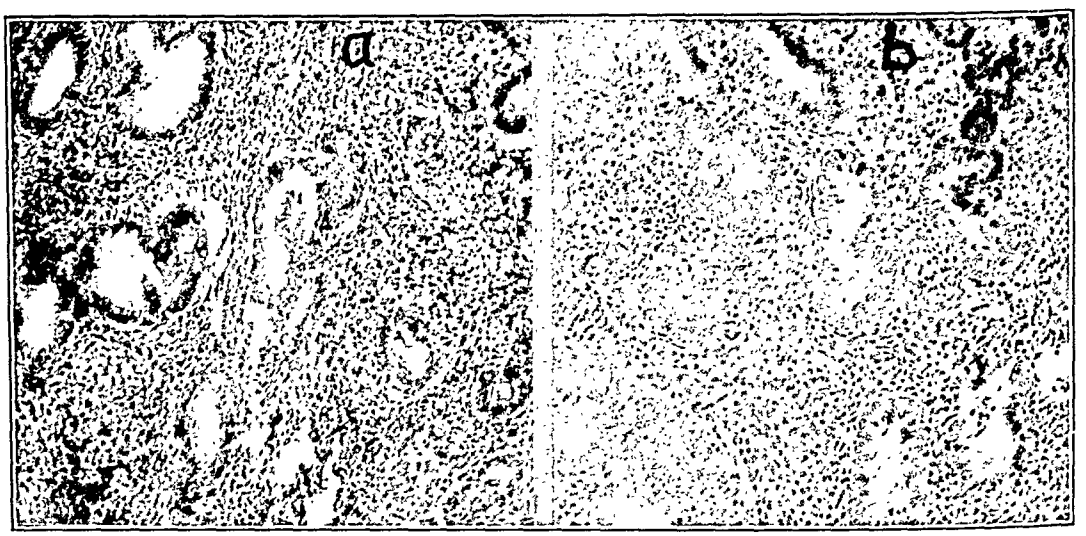


Fig. 6.—(*a*) Case R. J. Biopsy on twenty-third day of forty-one-day cycle, showing poor estrin activity, with irregular shapes and sizes of glands. Pregnancy followed therapy. (*b*) Case, S. N. Biopsy on twenty-eighth day of seven-week cycle, showing irregular glands, roughly simulating progestational effects, but with cellular characteristics of estrin action only. Pregnancy followed therapy.

R. J. was first seen at the age of 26 because of irregular and infrequent menses and sterility. Basal metabolism was within normal limits. She returned again at the age of 34 for the same reasons. Menstrual intervals were one to twelve months. Trial of thyroid had exaggerated nervousness. Some of the symptoms suggested a climacteric, and these were abated by the use of estrin (amniotin). This was discontinued after a few months. At the age of 38 she was seen again, when menses were occurring at four- to eight-week intervals. Endometrium obtained on the twenty-third day of a forty-one-day cycle showed glands of varying sizes, some dilated, but suggesting throughout the sections a low intensity of activity (Fig. 6, *a*). A retroversion, not previously present, was corrected with a pessary. Prephysin was used in 25-unit doses during the next 3 cycles, a total of only 18 doses being taken. Because of painful local reactions from the injections (early preparation, relatively crude), the treatment was discontinued. The next cycle was ended by a flow of only one day, and the patient reported nausea and breast symptoms very soon thereafter. A Friedman test made the diagnosis of pregnancy positive. Pregnancy was uneventful,

and was followed after two more years by a second successful pregnancy, with no more pituitary therapy.

The amount of therapy employed seems too small to account for the successful result, but the history and endometrial findings demonstrate that there was ovarian underactivity until pituitary treatment was used.

L. H. was seen at the age of 17 because of hirsutism and scanty flows of three to four days at six- to seven-week intervals. Use of thyroid, theelin, and emmenin produced no improvement. Amenorrhea for periods of five to twelve months were recorded, and pregnancy urine concentrate (follutein) was used, with 4 flows in six months. At this time the uterus was found to be distinctly infantile. She was married at the age of 18. After two years without treatment, at age of 20, the patient still had cycles at intervals of six to seven months, and was not able to become pregnant. Hypodermic injection of prephysin was started, using 25 unit doses for five days in the early part of each cycle. After 5 cycles, an endometrial biopsy was obtained, revealing only estrogenic hormone activity (Fig. 7, *a*), but followed six days later by a menstrual flow. The treatment was resumed, the number of doses increased to 10. Long menstrual intervals were decreasing, but regularity was not yet achieved. A second biopsy late in the fourth week of a cycle without treatment



Fig. 7.—Case L. H. (*a*) Biopsy on twenty-second day of twenty-eight-day cycle, with inadequate estrin activity. (*b*) Biopsy on twenty-fifth day of twenty-seven-day cycle after therapy, showing later results of progestin action.

revealed a well-developed progestational endometrium (Fig. 7, *b*). Treatment was continued in a somewhat irregular fashion for 4 more cycles, and after twelve weeks' amenorrhea an Aschheim-Zondek test demonstrated pregnancy. The patient went to term, and has a healthy child. After two more years without treatment menses have continued at thirty- to thirty-nine-day intervals without periods of amenorrhea, but without further test of fertility.

S. N. came for examination at the age of 33 because of loss of fertility after the birth of a first child at the age of 31 years. Menses had varied from one to three months in interval, five days' duration, with aching dysmenorrhea since the pregnancy. There were many climacteric symptoms present. A tendency to obesity had developed, accompanied by acne. The basal rate was 16 per cent above the normal. Pelvic examination discovered cystic and enlarged ovaries and a retroverted uterus, which was corrected by pessary. The endometrium obtained on the twenty-eighth day of a 7-week cycle showed a very low grade of estrogenic activity, without evidence of progestin action (Fig. 6, *b*). The patient was therefore started on hypodermic injections of gonadotropic material from pregnant mare serum (Gonadogen, Upjohn). After the use of 18 doses of 10 units each, the amenorrhea of ten weeks was shown to be due to pregnancy, and she delivered a healthy second child at term.

The amount of treatment seems too small to be responsible for the result, but the tissue showed distinctly that the ovarian activity was below expected levels, and the mechanical replacement of the uterus can hardly be held accountable for the entire result.

Results are not always so easily accomplished. Failure has been encountered, for example, in an otherwise healthy woman of 27 years, where endometrial biopsy on the twenty-fifth day of a twenty-seven-day cycle showed a poorly developed estrogenic hormone effect, followed by anovulatory bleeding. Increasing doses of prephysin to the point of 20 injections of 100 units each in a single cycle failed to make any definite increase in the intensity of the estrogenic influence on the vaginal epithelium. It was concluded that the ovaries were not susceptible of stimulation by the means available, as in the case of Z. R. reported in the first section of this paper.

A puzzling case is that of I. T., referred at age of 35 years because of sterility, followed by six months' amenorrhea after a long period of years with four-week type of menstruation. The husband has, of course, been examined and found to produce large numbers of motile sperm. Physical examination and history gave no unusual findings, and pelvic examination was not unusual. The study of vaginal epithelium showed low intensity of estrogenic hormone activity. Gonadogen was given in 20 unit doses, 5 times in the first two weeks of the cycles, with improvement in regularity of flow but little increase in estrogenic response shown in the vagina. After two cycles with increase to 15 daily doses of Gonadogen there was more evidence of estrin action. During the fourth week of the cycle twenty-four-hour urine specimens were examined and found to contain 45 mg. pregnandiol glycuronidate in seven days, within normal expectations. Treatment was a bit irregular, amenorrhea occurred, but Aschheim-Zondek test made pregnancy unlikely, and the injections were resumed. The estrin activity continues to follow the treatment, sometimes approaching, but not equalling the normal expectancy of the second week of the cycle. Nevertheless five months' amenorrhea, without pregnancy leaves an unsatisfactory result. The problem is to determine the exact dosage needed to re-establish normal intensity of ovarian action. This may be beyond clinical judgment with present methods for quantitative estimation of the needs.

PRIMARY AMENORRHEA

Complete absence of menstrual function in an adult woman presents not only a test of the adequacy of gonadotropic therapy, but also the problem of determining whether the deficiency is due to lack of pituitary stimulation or lack of ovarian tissue which can respond to the stimulus. The methods already described can contribute to decisions on both aspects of the problem, as shown by the following two cases.

N. S. was admitted to the psychiatric service at age of 25 because of numerous phobias, and a complicated personality problem involving great reticence about sex matters, extending even to refusal to permit bimanual pelvic examination by a woman physician. There had never been a menstrual flow. Acne, obesity, small breasts, and a masculine escutcheon were the only important physical findings. The basal rate was 8 per cent above normal. A woman assistant finally won her confidence sufficiently to secure vaginal epithelium samples with a pipette. These showed cells and debris typical of the castrate condition (Fig. 8, *a*). It was not certain that there were any ovaries. She was given 15 daily doses of 25 units each of prephysin, during which time a marked change appeared in the vaginal material, including the occurrence of reduced numbers of leucocytes, less mucus and debris, and the desquamation of typical cornified cells (Fig. 8, *b*). There was a flow of blood stained material for one week, beginning five days after this series was completed. During this period of treatment, there was a marked improvement in the psychic condition, which has continued subsequently, making it possible for the patient to secure and keep employment.

Similar treatment was continued at home for 6 series of prephysin injections, but only a slight flow occurred, for one day on the twenty-second day after the first had appeared. Eight months later, on request, the patient returned and permitted examination under anesthesia, and the uterus was found to be small. Tissue obtained by curette showed low intensity of estrogenic stimulation, resembling the "Swiss cheese" hyperplasia with irregularly dilated glands in some areas (Fig. 8, *d*). There were two brief flows ten and seventeen days later, after resuming use of prephysin in 100 unit doses. The immediate result of this stimulation was not greater,

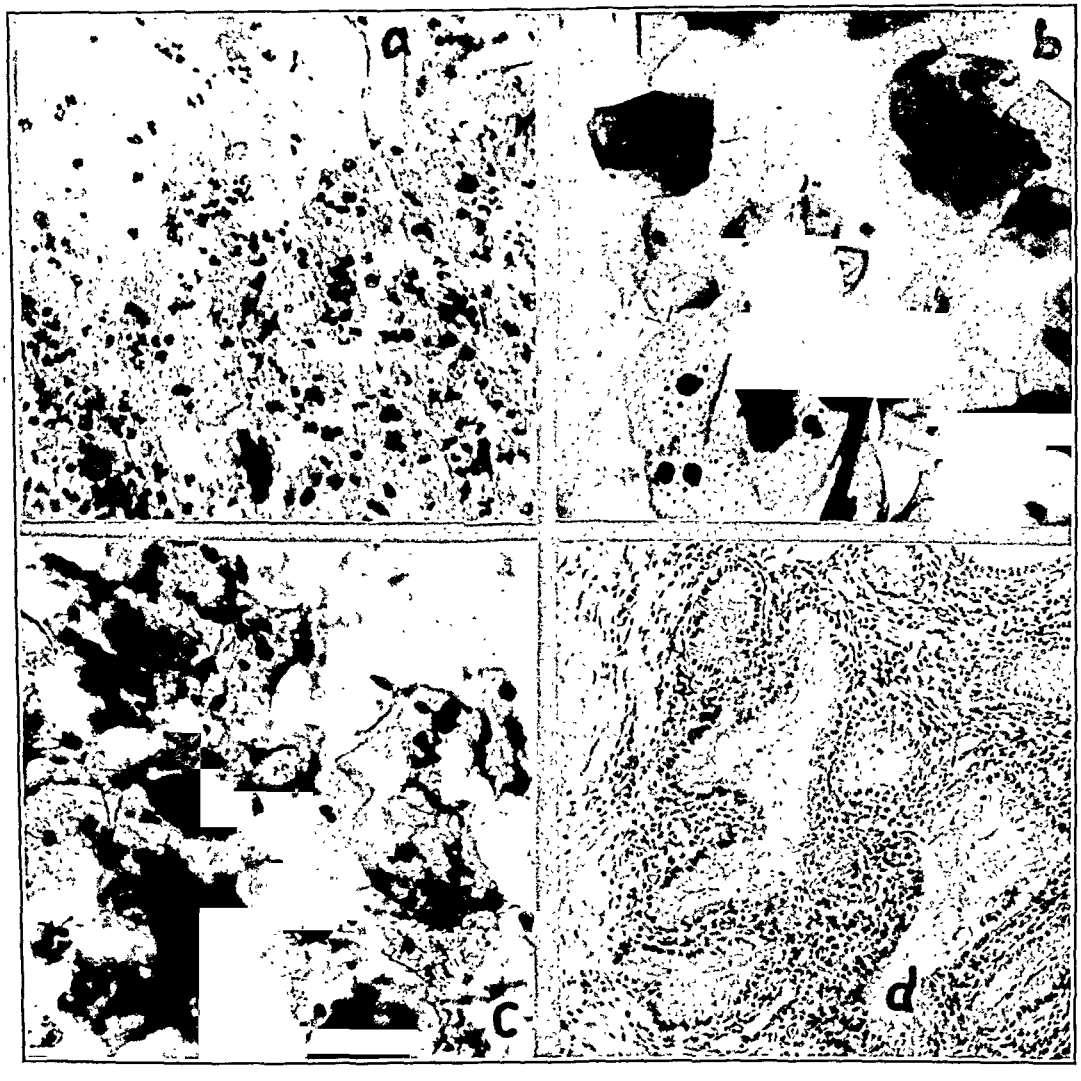


Fig. 8.—Case N. S. (*a*) Vaginal smear before therapy, showing the small deep layer cells, leucocytes, degenerating epithelial cells and debris. (*b*) Smear after ten days' treatment with prephysin, showing production of normal type vaginal squamous cells; beginning of cornification, and clearing of the field. (*c*) Smear taken after three months without treatment, showing some regression but presence of superficial type cells demonstrating continued low intensity of estrin action. (*d*) Biopsy obtained at same time as (*c*), showing irregular size and shape of glands in endometrium, from low intensity, sustained estrin action.

judged by vaginal epithelium, than the first use of 25 unit doses. In spite of 6 cycles of monthly treatment, using 10 and later 15 doses of 100 units each, the tissue response was not improved, but there was sustained psychic development toward a healthy attitude. After three months without treatment the vaginal reaction still showed some evidence of activity, and treatment was resumed using the gonadotropic pituitary extract of Armour, 300 Collip units per c.c. daily for fifteen days. With the use of this preparation subjective improvement was resumed about as promptly as with the previous use of prephysin. To date no further flows have

appeared. So far 4 flows have occurred in nineteen months, not a perfect record, but there has been obvious psychic improvement, the breasts have begun to develop, and it has been proved that there is ovarian tissue which can respond to artificial stimulation. The value of continued treatment is questionable. One can hardly hope to produce development to the point of fertility, and this may not be desirable. The social value of the results so far make the therapy worth while from both the point of view of the patient and the physician.

G. F. requested advice at age of 20 because of primary amenorrhea. Her only other complaints were of hot flashes, occasional vertigo, and small breasts. Basal metabolism was 6 per cent above the normal level. Under anesthesia the uterus was found to be small and retroverted. No endometrium could be obtained with a curette. She was started at once on use of 100 unit doses of prephysin daily for ten days, followed by similar doses on alternate days for twenty days. This series was repeated for 5 cycles without subjective change. The only alteration in the vaginal epithelium was the apparance of "mucified" cells on two occasions. No flow was recognized. Therapy was changed to the use of gonadogen, 10 unit doses given daily. The result was a more definite stimulation as judged by slight cornification of vaginal cells, and a brief menstrual flow appeared after the second series of 10 doses of 20 units each. The response, although slow in appearing, demonstrates again the presence of ovarian tissue which can be stimulated. Large doses and sustained therapy are required. Continued use of series of 20 doses, totaling 300 units, given over periods of twenty-five days, repeated each month, has failed to induce further flowing, or more marked vaginal epithelial cell response.

DISCUSSION

As instruments for diagnostic study and the estimation of the progress under therapy, the curette and the biopsy punch have advantages which make each of them necessary. For elimination of neoplastic disease the curette is indispensable. With infantile uteri the curette is still the only way to secure tissue at times. But in making examinations where the progress of the cycle is not to be interrupted, where prolonged hospitalization is impossible, or where repeated examinations are desired the biopsy technique is superior. We have not yet seen significant differences between biopsy specimens taken at different areas *above the cervix* at the same sitting. There is more variation between specimens taken at different depths beneath the lumen of the uterus. With attention to this feature, there is little risk of mistaking the effects of estrin and progestin in the endometrial glands.

The Papanicolaou and Shorr technique[2] for examining vaginal epithelium gives information similar to that obtainable by the vaginal biopsy method of Davis,[6] but with obvious advantages. Specimens are taken frequently by the patients, and brought in for examination. This makes possible study of changes from day to day when desired. The results are interpretable only in terms of estrin action, without evidence of progestin effect. To meet this deficiency the use of the pregnandiol determination in serial twenty-four-hour urine specimens is the best method, unless endometrial biopsies are obtainable. The biopsy approach is easier for the gynecologist, requires less laboratory time, but is frequently not welcomed by the patient. One further great advantage of pregnandiol estimation is the possibility of quantitative determination of the intensity of progestin secretion. It is difficult to estimate deficiencies of estrin or progestin action from the study of the biopsy specimens unless gross deficiency exists. Probably the success of a program

of treatment will be found increasingly to depend on the quantitative criteria for estimating progress. This has been the case in other endocrine disorders, such as thyroid deficiency, diabetes mellitus, tetany, and the climacteric.

The results presented at this time are selected from the patients studied for a sufficiently long time to make possible some judgment as to the adequacy of therapy. It will be evident that progress could have been measured more definitely and decisions made sooner in some cases if the vaginal epithelium and pregnandiol techniques had been freely available in the earlier years. More frequent use of biopsies has been limited by the cost of hospitalization for the purpose. Increasing experience with this technique, with no unfortunate consequences after hundreds of biopsies, makes office biopsy by experienced gynecologists a safe procedure.

We are still of the opinion that diagnoses as to the cause of amenorrhea, irregular menses, menorrhagia, and sterility cannot be made by any combination of history taking, physical examination, and pelvic examination, with ordinary laboratory tests. The use of the microscopic study of endometrium, or at times of the vaginal epithelium and the pregnandiol excretion give information of prime importance. Without such data diagnoses are inaccurate, and therapy is empirical. Such examinations are to precede the use of expensive and potent endocrine materials. To determine progress the history of menstrual flowing is likewise inadequate, unless fortified with similar examinations.

It is still all too evident that the need is for more potent as well as purified pituitary preparations. Some cases respond sufficiently to the extracts now available. As these quantitative concepts of ovarian activity are applied to individual cases it will become easier to vary treatment to fit the patient's needs, and also to decide at an early date which patients will probably not benefit from endocrine therapy.

There has been too little experience to judge the relative merits of the various pituitary preparations we have employed. Our major experience has been with prephysin (Chappel Laboratory). This is made from sheep and horse pituitaries. A small experience with gonadotropic antuitrin (Parke, Davis and Co.) reveals that this is active, but too low in potency for most uses. It is a hog pituitary extract, not yet released for sale. The trials of gonadogen (Upjohn Laboratory) have been distinctly encouraging. This is a preparation from the serum of pregnant mares, standardized in a large unit, which makes comparison with the other materials difficult. It has the advantage of being a dry preparation of great permanence, readily dissolved for injection, and so well purified that it causes less local reaction than other gonadotropic materials. Our use of the gonadotropic extract (Armour Laboratories) is too recent to warrant anything except the statement that it is apparently a safe material. The unit of standardization (Collip) is roughly one-tenth that used for prephysin. Large numbers of units must therefore be employed to secure clinical results.

We have deliberately presented cases demonstrating success, partial success, and failure following endocrine treatment. This series does

illustrate what may be expected from endocrine therapy in properly selected cases. These methods avoid both the ordinary hazards of surgery and the dangers of loss of function from the removal of ovarian and uterine tissue so often considered necessary in treating menorrhagia in the past.

SUMMARY

From an experience with use of genuine pituitary gonadotropic extracts for seven years, we are reporting examples of the results which may be expected in treating women for primary or secondary amenorrhea, for menorrhagia and irregularity of menstrual cycles, and for relief of sterility. All the syndromes presented here are considered to be the result of underactivity of ovarian hormones, dependent presumably upon underactivity of the anterior pituitary in supplying gonadotropic hormones. For accurate diagnoses and conduct of treatment the use of endometrial biopsy and vaginal epithelial samples secured by pipette, as well as of pregnandiol determinations in urine, are shown to be important aids. If these aids fail to show definite response to treatment, even though menstrual flows are occurring at fairly regular intervals, the treatment may well be increased or abandoned. The use of long series of repeated daily doses, extending for five to 15 days at the beginning of each menstrual cycle, seems necessary and is demonstrated to be safe. Results are not achieved in a single month. This study indicates the need for individualization of dose, and for the preparation of more concentrated pituitary extracts.

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From a study of 79 cases of dysgerminoma reported in the literature and investigation of 19 instances available in the laboratory of Johns Hopkins Hospital, the author concludes that this newgrowth, representing less than 3 per cent of all malignant ovarian tumors, is relatively rare. It occurs in young persons usually under 30 years of age. It appears as a rapidly growing elastic, nodular mass in the adnexal region. In the more malignant types the retroperitoneal glands, peritoneum, omentum, bladder and rectum rapidly become involved through metastases, which rarely appear in distant organs. Dysgerminoma may be associated with other forms of ovarian tumor.

These newgrowths have a mortality between 35 and 60 per cent, with a slightly higher rate of recurrence and metastasis.

The treatment of choice is removal of the growth with adjoining tube. If removal is impossible the patient should be given the benefit of irradiation.

HUGO EHRENFEST

VARIATIONS OF LIPOID CONTENT IN CERTAIN OVARIAN TUMORS*

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INTRODUCTION

THUS far, chemical investigations of tumors have detected little that indicates any marked deviation of the chemical processes of tumor cells from those of normal cells of similar origin. This is significant particularly when it is coupled with the fact that tumor cells have the capacity to produce complicated products of metabolic action specific for the parent cells from which they arose. Witness adenomas of the islets of Langerhans or metastatic carcinoma of the thyroid.

In applying these principles to the study of lipoids in certain ovarian tumors, much information may be gained, which, if properly evaluated, may become an open sesame permitting inquiry into the very origin of tumor cells. For here in these ovarian neoplasms the tumor cells seem to contain the same fats, lipoids, and chemical (hormonal) activity as the normal cells from which the tumors arose.

We, therefore, present this study in which allusion is made to the content and distribution of fats and lipoids in a group of ovarian tumors.

LIPOIDS IN GRANULOSA CELL TUMORS

CASE 1.—Fig. 1 is a frozen section from a mature homogeneous type of granulosa cell tumor, stained with sudan III and hematoxylin. Note the island of granulosa cells with its striking periepithelial garland of lipoid laden stroma cells. The granulosa cells contain very minute protoplasmic sudanophilic droplets. Deposited in the connective tissue core that here and there invaginates the epithelial plug of granulosa cells are occasional aggregates of large coarse lipoid droplets. The cells of the connective tissue stroma immediately adjacent to the epithelial mass are large, swollen, heavily laden with very fine intensively staining sudanophilic granules and droplets. This thecalike reaction of the stroma suggests the probability that granulosa cells exert a profound influence on the connective tissue immediately in contact with it. The chemical activity (hormonal) of the neoplastic granulosa cells, as reflected by its lipoid deposition, is analogous to the normal maturing follicle just prior to rupture when the granulosa cells show but minimal luteinization in contrast with the abundant lipoid accumulation in the theca interna.

CASE 2.—Fig. 2 is a frozen section from an immature trabecular type of granulosa cell tumor stained with sudan III and hematoxylin. The illustration shows the partial condensation of the solid masses of mesenchyme into trabecular structures. The lipoid distribution follows no particular pattern. Large globules of fused fat droplets are found extra- and intracellularly here and there among the cells comprising the immature trabeculae. The undifferentiated connective tissue stroma shows a nondescript minimal scattering of lipoid droplets. The lipoids when studied with the polariscope are noncrystalline and non-refractile although

*Presented before the Chicago Gynecological Society, October 21, 1938.

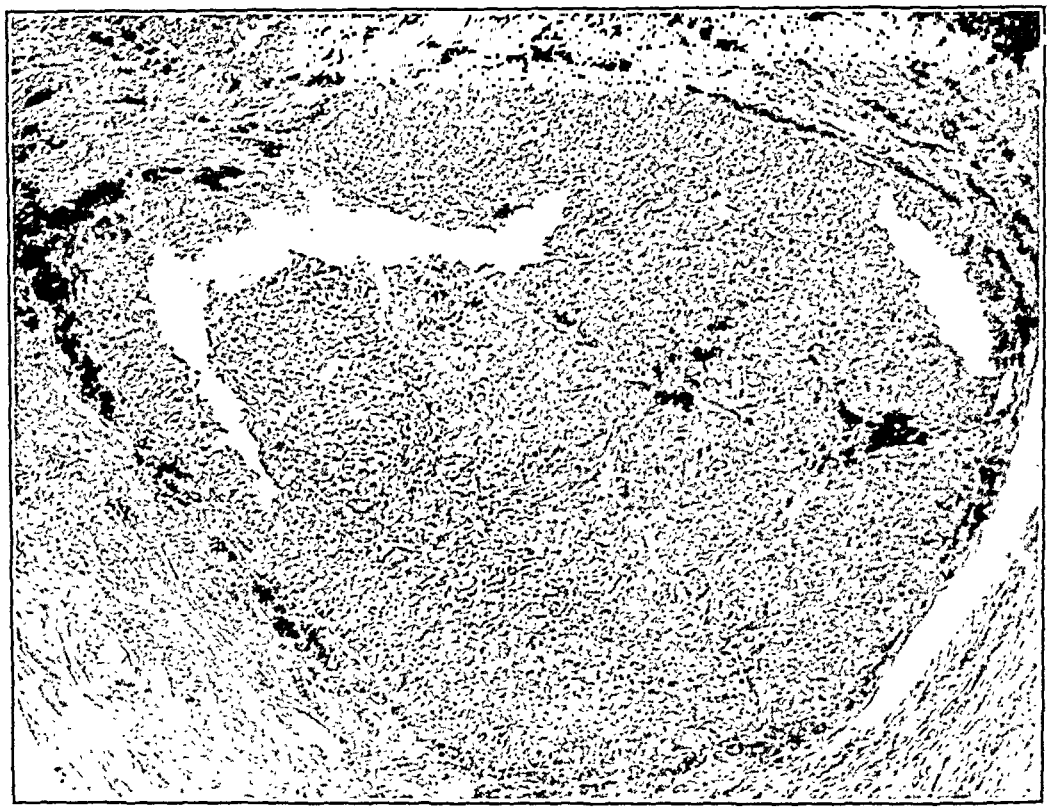


Fig. 1.—Case 1. Granulosa cell tumor (mature homogeneous type). Note the periepithelial accumulation of lipoids (stained black) in the stroma simulating a thecalike reaction. (Sudan III-hematoxylin stained frozen section ×150.)

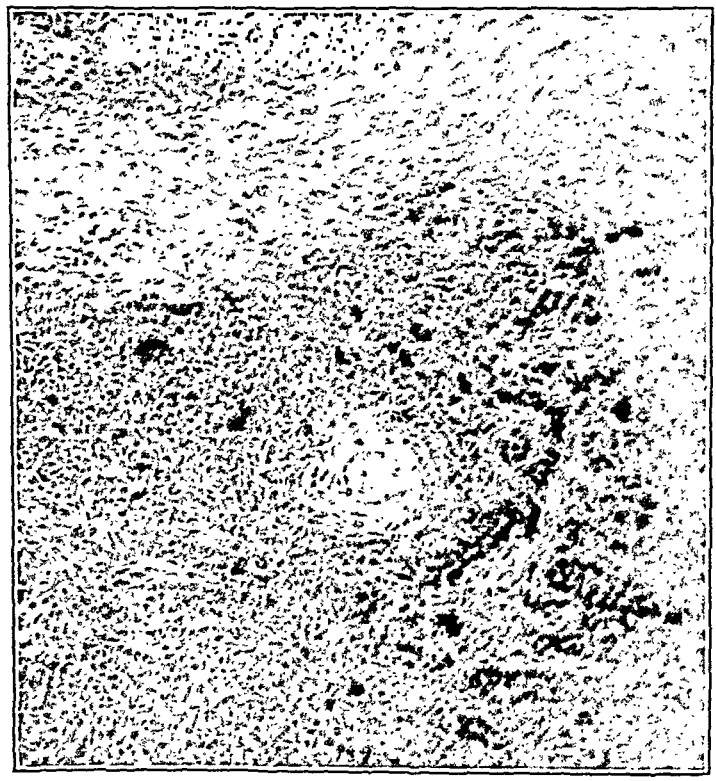


Fig. 2.—Case 2. Granulosa cell tumor (immature trabecular type). Note the lipoid distribution (black globules). (Sudan III-hematoxylin stained frozen section ×280.)

an occasional birefringent crystal is observed. The lipoids in this tumor are quite variable, for their presence is not encountered in all sections under study.

LIPOIDS IN THECA CELL TUMOR

CASE 3.—Fig. 3 is a frozen section from a thecoma stained with sudan III and hematoxylin. This illustration typifies the lipoid distribution in truly luteinized (pseudo) theca cell tumors. Large sheaves of connective tissue cells are surcharged with intracellular sudanophilic granules. Occasionally the lipoids are in the form of larger droplets, some of which may be found extracellularly. The intensity of the lipoid accumulation as brought out by the sudan-staining reaction varies in different areas of the same tumor. Some sheaves contain moderate to negligible amounts of sudanophilic lipoids. The dense white fibrous connective tissue core forms the matrix of the tumor. This may be abundant, altogether lacking, or comprise the greater part of the tumor. The lipoids are frequently more abundant

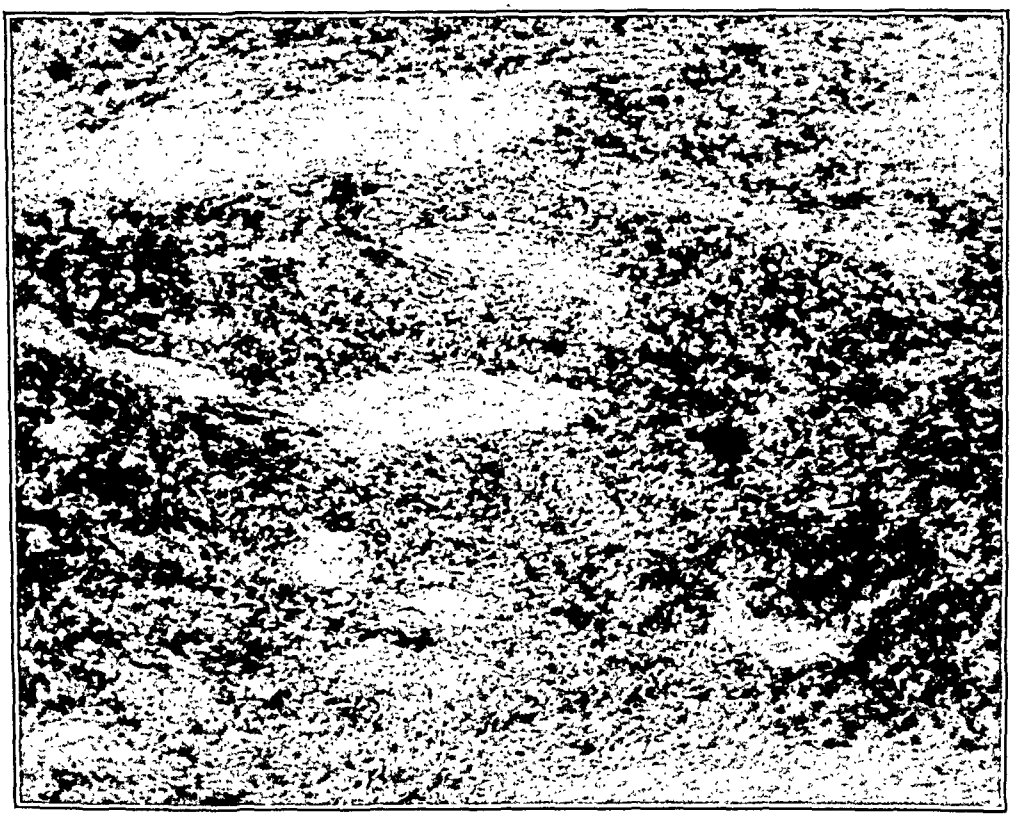


Fig. 3.—Case 3. Theca cell tumor. Note the sudanophilic droplets stained black in illustration. (Sudan III-hematoxylin stained frozen section low power.)

where the fibrillar connective tissue cells take on a plump fusiform epithelioid character. The fats, when studied with the polarizing microscope, show a marked abundance of refractile lipoids. They are for the greater part doubly refractile, i. e., anisotropic lipoids; biaxial, and show oblique extinction.

In the normal ovary the counterpart of the cellular component of this tumor is found in the proliferating connective tissue that takes on thecalike properties in the formation of an atretic follicle or in the cells of the theca interna participating in corpus luteum formation. Because of the intense sudanophilic character of the lipoids and the desmogenic nature of the constituent cells, these tumors have been designated xanthofibroma theca cellulare.

CASE 4.—Fig. 4 is a frozen section stained with hematoxylin and sudan III from a "theca-granulosa" cell tumor previously reported by us (J. P. G. and R. B. G.)[1] in this JOURNAL. The epithelial plug of granulosa cells contains a comparatively meager amount of lipochromic granules. The stroma in juxtaposition to this mass

of granulosa cells shows marked sudanophilic accumulation. Surrounding the epithelial nest is a broad zone of fibromatous tissue composed of plump fusiform cells, which in part is so intensely sudanophilic that on gross inspection of the section it appears as a massive tomato red area in color. On studying these sections with the polarizing microscope, an abundance of refractile lipoids is found in the fibromatoid part of the tumor; these are, for the greater part, birefringent. Most of the birefractile crystals are biaxial and show oblique extinction; a few show parallel extinction. The fats in the epithelial plugs show a smaller amount of refractile lipoids, but these are mostly isotropic. Here side by side are neoplastic granulosa and theca cell components in the same tumor, the counterpart of which is to be found in the normal ovary, in the ripening Graafian follicle with its periepithelial garland of theca cells. That granulosa-theca cell tumors



Fig. 4.—Case 4. Granulosa-theca cell tumor. Note dense sudanophilic fibromatoid tissue surrounding a focal mass of granulosa cells (upper left). (Sudan III-hematoxylin stained frozen section ×135.)

occur more frequently than is at present appreciated is quite probable, for in the embryonic development of the ovary, granulosa cells are formed in loco from ovarian mesenchyme as are likewise the thecal and stromal tissue. In 1882 Maffucci recorded the details of an ovarian tumor in which granulosa and theca cells were predominant.[2]

LIPOIDS IN ARRHENOBLASTOMA

CASE 5.—Fig. 5 is a frozen section of the trabeculated type of arrhenoblastoma stained with sudan III and hematoxylin. The mesenchyme attempts to form germinal cords; lipoid deposition in the tumor is limited to the Leydig cells accompanying the cords. The prototype of this tumor may be found in the male fetus as early as five and six months when the Leydig cells laden with fat accompanying the trabeculae make their appearance in the male gonad. The lipoids in arrhenoblastoma are limited in a great measure to the cytoplasm of the Leydig cells. Only a small part of these fats are refractile, and these are usually birefringent, showing oblique extinction.

LIPOIDS IN HYPERNEPHROMA OF THE OVARY

CASE 6.—Fig. 6 is a frozen section from a hypernephroma of the ovary stained with sudan III and hematoxylin. This neoplasm is very cellular. Large sinusoids demarcate the tumor into large cellular zones. The constituent cell is large with a proportionately large nucleus and nucleolus. The cytoplasm is spongy, containing an abundance of sudanophilic lipoids. The distribution of the lipoids, however,



Fig. 5.—Case 5. Arrhenoblastoma—trabecular type. Sudanophilic Leydig cells accompany the condensation of the mesenchyma into cordlike structures. (Sudan III-hematoxylin stained frozen section ×240.) (Courtesy of W. Schiller.)

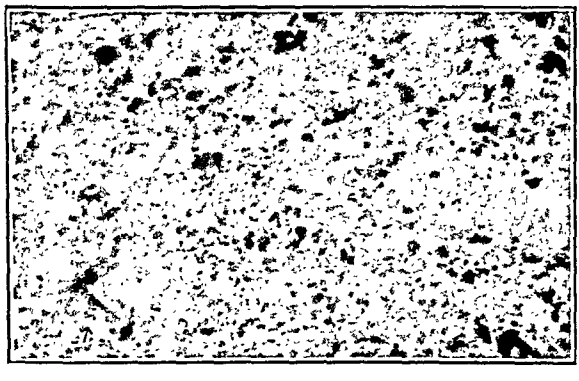


Fig. 6.—Case 6. Hypernephroma of ovary. Note the lipoid distribution. Arrow points to typical lipoid crystals found in abundance in this tumor. (Sudan III-hematoxylin stained frozen section ×300.)

is very irregular, being more pronounced in the vicinity of the sinusoids. The fat is in the form of large, bright red lipoid cytoplasmic globules, or large, bright yellow extracellular lipoid crystals. The latter are particularly noteworthy; they appear to be oblong acicular crystals, arranged in bizarre fashion, frequently in fasciculated bundles or piled upon one another to give a laminated appearance, or arranged in groups at an obtuse angle. Some of these are well illustrated near the left border in Fig. 6. The sections when studied with the polarizing microscope exhibit an abundance of refractile lipoids. Some of the large crystals just

described are isotropic; the larger number, however, are doubly refractile and show biaxial oblique extinction. When stained with Nile blue, the cytoplasmic globules are royal blue and the extracellular crystals pinkish yellow.

In the classification of this neoplasm much controversy exists. Opinions confine it to the luteinizing granulosa cell tumors, the luteomas or the hypernephromas. Sections of normal corpus luteum, adrenal, hypernephroma of the kidney and suprarenal cortical adenoma were studied with sudan III and Nile blue stains. It is worthy of note that only in the suprarenal cortical adenoma are there to be found lipoid crystals that are identical with those observed in the hypernephroma of the ovary. The Nile blue stain brings forth an abundance of similar pinkish yellow crystals. These crystals, that are peculiar to both the hypernephroma of the ovary and suprarenal cortical adenoma, not only have comparative morphologic features and staining reactions, but also identical polariscopic characteristics. The lipoid study of this tumor supports the contention that its cells are derived from misplaced suprarenal nests in the ovary.

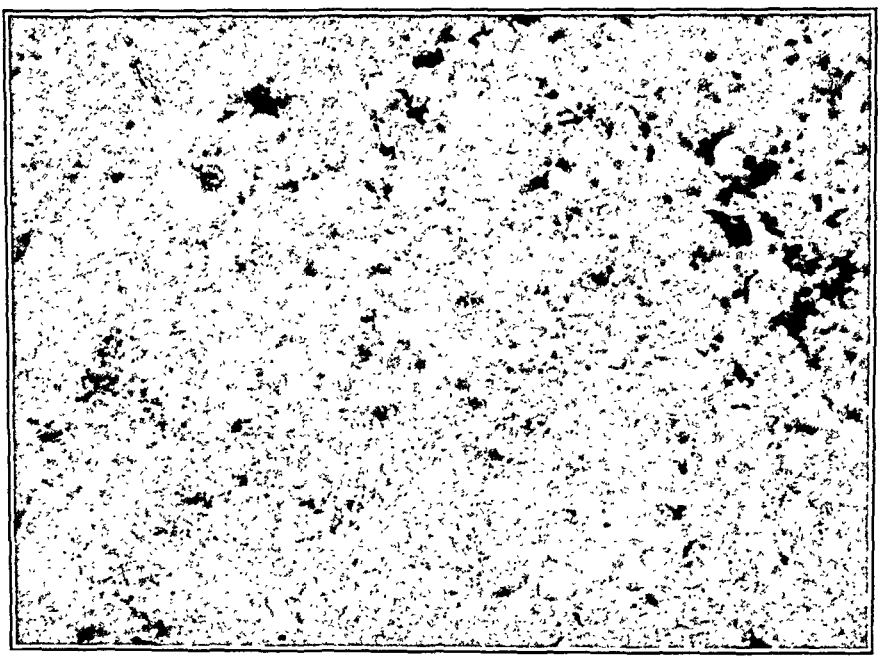


Fig. 7.—Case 7. Krukenberg tumor. Note abundance of lipoids present. (Sudan III-hematoxylin stained frozen section ×300.)

LIPOIDS IN A KRUKENBERG TUMOR

CASE 7.—Fig. 7 is a sudan III—hematoxylin stained section of a Krukenberg tumor. The lipoids are found haphazardly distributed and exist both as intra- and extracellular fat droplets. The fat, when studied with the polarizing microscope, proves to be nonrefractile. With the Mucicarmin stain an abundance of mucin distending the cytoplasm of the signet cells is apparent. Geist[3] recently pointed out that one so-called luteoma reported in the literature, that he had occasion to examine, turned out to be a Krukenberg tumor. It is evident that the error in diagnosis could be attributable to the large amount of lipoids present in this so-called luteoma to warrant the possibility of such a diagnosis. Since Krukenberg tumors may contain lipoids, this finding proves that lipoids are not a distinctive feature of the endocrine group of ovarian neoplasms.

LIPOIDS IN A FIBROMA

CASE 8.—Fig. 8 is a sudan III—hematoxylin stained section of an ovarian fibroma. The deposition of sudanophilic droplets is found particularly in the vicinity of nests of fibrous connective tissue cells rather than in the mature collagenized or hyalinized zones. Certain aspects in the clinical history of this case would

suggest the possibility of a thecoma. The patient had menorrhagia of two and one-half weeks' duration during each month with accompanying breast enlargement. After removal of this large unilateral tumor, the menses were reduced to a regular three-day flow, and the patient ceased to experience the cyclic breast enlargement. The great variation in the cellularity of the tumor, the collagenized zones, and the presence of fats in the tumor are also suggestive of thecoma. However, on polariscopic examination, the lipoids are nonrefractile, thus differing from the lipoids in theca cell tumors.

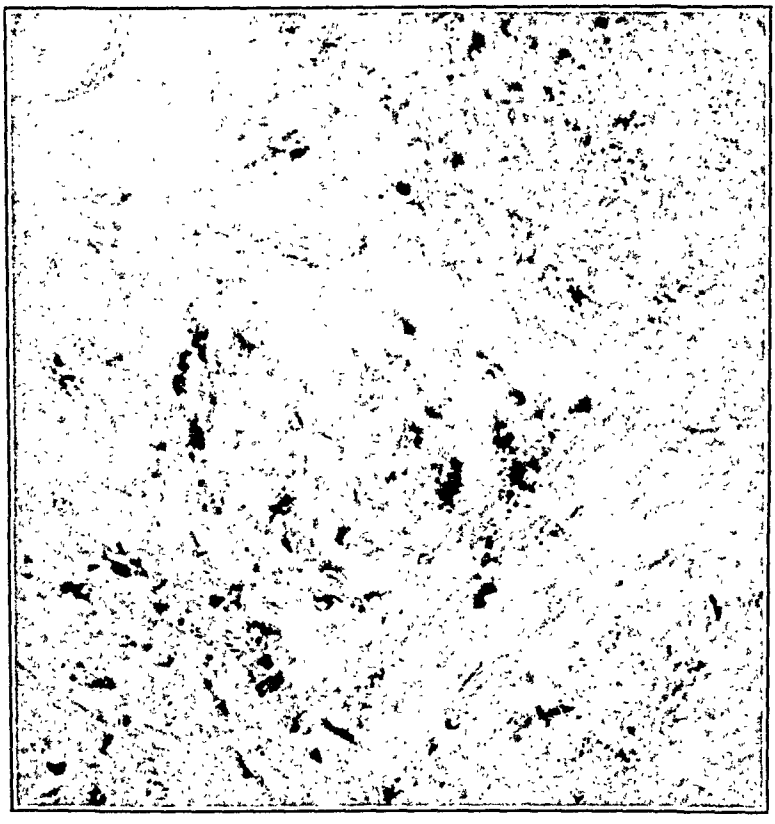


Fig. 8.—Case 8. Fibroma of the ovary. Note the lipoid deposition. (Sudan III-hematoxylin stained frozen section ×280.)

TECHNIQUE AND ANALYSIS

In an attempt to establish some basic facts concerning the lipoids in ovarian tumors, extractions and chemical analyses of the fat content were performed in eleven of the tumors in our series. Sections of tissue were taken from the best preserved portions of the tumor. The tissues were minced, weighed, and extracted for several hours, depending upon the size of the sample, with hot alcohol in a Sohxlet extraction apparatus. The alcohol extract was evaporated carefully to dryness and the residue extracted several times with small portions of ether. The ether extracts were combined, made to volume and an aliquot portion taken for analysis. The total lipoid material was determined by evaporating an aliquot portion of the ether extract and weighing the residue. This residue was taken up in chloroform. The chloroform extract was divided, one part being used for the determination of cholesterol, the remainder for the estimation of lipoid phosphorus.

In Table I, the term "total lipid" denotes the weight of the alcohol soluble material which was also soluble in ether. The "phospholipid"

values were arrived at by determining the total phosphorus in the chloroform extract above by the Briggs method. The amount of phosphorus was multiplied by 25.1 to get the charted values. Cholesterol was determined colorimetrically by the acetic anhydride method. The term "lipid residue" denotes the alcohol-ether soluble material not accounted for as cholesterol and phospholipid. In Table I the 11 tumors studied by chemical analysis are divided into 2 chemical groups. The incretory group (1 to 7) supposedly yields telltale evidence of some endocrine disturbance. In this group there are 4 granulosa cell tumors, 2 theca cell tumors, and 1 hypernephroma of the ovary. The nonincretory group (8 to 11) is supposedly without endocrine significance. In this group there are 2 fibromas, 1 Krukenberg tumor, and 1 probable rete cell tumor. It is noted that in the incretory group the phospholipid content ranges from 0.31 to 1.88 gm. per cent and the cholesterol levels from 0.34 to 1.27 gm. per cent of wet weight. One fact is singularly brought out by analysis of this table and that is the comparatively low values for phospholipid (0.08 to 0.27) and cholesterol (0.02 to 0.29) in the non-incretory group. These values unequivocally permit the division of these tumors into two clinical groups.

TABLE I. PERCENTAGE OF LIPOID MATERIAL

DESCRIPTION OF OVARIAN TUMORS	WEIGHT OF TISSUE GRAMS	TOTAL LIPID GRAMS	PER CENT OF WET WEIGHT			
			TOTAL LIPID	PHOSPHO-LIPID	CHOLES-TEROL	LIPOID RESIDUE
1. Granulosa cell (mature homogeneous)	0.57	0.024	4.21	0.78	0.46	3.00
2. Granulosa cell (mature homogeneous)	6.27	0.328	5.23	0.93	0.34	3.96
3. Granulosa cell (immature trabecular)	4.60	0.126	2.74	0.92	0.68	1.14
4. Granulosa cell (mature trabecular)	1.30	0.043	3.31	0.31	0.57	2.43
5. Thecoma (cellular)	0.79	0.039	4.94	0.60	1.05	3.28
6. Thecoma	2.11	0.040	1.89	1.19	0.41	0.29
7. Hypernephroma	0.97	0.035	3.63	1.88	1.27	0.48
8. Rete cell (?)	33.00	0.357	1.08	0.27	0.29	0.52
9. Krukenberg	57.10	2.452	4.29	0.23	0.29	3.77
10. Fibroma	44.10	0.144	0.33	0.08	0.02	0.23
11. Fibroma	50.80	0.336	0.66	0.22	0.12	0.31
Thecoma (Geist)	109.00	2.990	2.70	0.32	1.10	1.28

In evaluating the one thecoma chemically analyzed by Geist,[4] we find his rather high value for total cholesterol, i.e., 1.10 gm. per cent was matched by one of our thecomas, i.e., 1.05 gm. per cent when compared to the ratio of cholesterol to total weight of tissue. The fibromas under study showed lipoid accumulation when stained with sudan III and in a measure simulated thecomas morphologically. However, the polariscopic features of these lipoids and their low cholesterol values on chemical analysis rule out their consideration as thecomas.

The granulosa cell tumors listed in the table as 1 and 2 resembled each other morphologically, both being of the mature homogeneous type. Frozen sections stained with sudan III yielded similar reactions. It is significant that the close comparative values obtained on chemical analysis corresponded to their morphologic similarity.

DISCUSSION

In our series of solid ovarian tumors studied with special lipoid stains there were included granulosa cell tumors (5), theca cell tumors (2), arrhenoblastomas (4), disgerminomas (4), Brenner tumors (2), Krukenberg tumors (2), fibromas (5), fibromyomas (2), fibrosarcoma (1), adenocarcinomas (2), as well as a hypernephroma of the ovary, a combined granulosa-theca cell tumor, and a possible rete cell tumor of the ovary. It seemed that fat may be encountered in ovarian neoplasms (exclusive of dermoids and teratomas) in at least three distinct conditions: (1) as a degenerative process, (2) as an inherent capacity of certain embryonal mesodermal tissue, and (3) as a product of tissue metabolism (hormone storage).

In disgerminomas there may be found, in more or less abundant numbers, large macrophagic cells filled with sudanophilic lipoids. These cells appear more numerous in the vicinity of necrotic areas. The fat is nonrefractile and probably degenerative. In Krukenberg tumors, fibromas, fibromyomas, etc., the lipoid deposition may be marked and is present in the form of intra- and extracellular sudanophilic granules and droplets or large fused globules. Brenner tumors show a meager amount of fat and this is found in the fibromatous tissue as minute round lipochromic granules resembling streaks of fine reddish sand. About some of the squamous cell nests, these fine granules are occasionally more prominent. It appears that the lipoids in this group are part of a degenerative process.

The question arises as to what significance may be attached to the presence of lipoids in the incretory group of ovarian tumors. Does the presence of lipoids actually represent storage of hormones? The granulosa cell tumors not only vary greatly in their morphology but vary just as widely in their fat content, and yet have a predominantly similar clinical syndrome, that of estrogen stimulation. It has been assumed that granulosa cell tumors contain comparatively minor amounts of lipoids and that these are phospholipid in nature (Melnick and Kanter[5]). It has long been known that some granulosa cell tumors undergo extensive luteinization (pseudo). In 1910 Lécène[6] recognized a type of granulosa cell tumor rich in fats and lipoids, which he termed "folliculome lipidique." Moulonguet[7] and Plate[8] have reported similar cases. In Moulonguet's case there was an abundance of double refractile lipoids, i.e., cholesterol and cholesterol esters. Loeffler and Priesel[9] separated from the granulosa cell tumors, the xanthofibromas, a desmogenic group rich in lipoids. It has been shown that a goodly amount of the fats in this group, now commonly referred to as thecomas, is in the form of doubly refractile lipoids, i.e., cholesterol esters. In the combined granulosa-theca cell tumor re-

ported by us the doubly refractile fats were particularly abundant in the fibromatoid part of the tumor. It appears that both granulosa cell and theca cell tumors give more or less identical clinical syndromes in spite of the fact that on polariscopic study the amount of doubly refractile crystals may be minimal, or lacking in one and abundant in the other. The chemical analysis of these tumors, however, shows that both have quite an amount of total cholesterol, though this value tends to be much higher in theca cell tumors.

What influences the deposition of an abundance of lipoids in certain of the incretory tumors, and not in others? When granulosa cell tumors contain an abundance of lipoids they are spoken of as luteinized granulosa cell tumors. Theca cell tumors contain an abundance of lipoids, and by the same token are luteinized theca cell tumors. The evident corollary presents itself that theca cell tumors may well exist that are not luteinized, just as theca and potential theca cells exist in the normal ovary. In this series one fibrosarcoma of the ovary on microscopic study (in reality a very cellular fibroma) exhibited every characteristic that is generally attributed to the thecoma, except that with sudan III stain, lipoids were not demonstrable and clinically did not yield endocrine disturbances. Traut and Butterworth[10] have done some excellent experimental work on mice, and have suggested that there exists an undifferentiated (unluteinized) and a differentiated (luteinized) type of theca cell tumor. By irradiating the mouse ovaries these authors have produced granulosa cell tumors as well as so-called luteomas. They concluded, however, that "luteomas are formed by luteinization of the granulosa cell tumors thus produced."

One point should be made clear; the abundance of lipoid in the incretory tumors does not necessarily mean luteinization. Lipoid deposition and luteinization are not synonymous (Varangot[11]). Luteinization is mirrored in the endometrium by the production of a secretory phase. The endometrial studies in most of the thecomas, so-called lutein cell tumors (luteomas) and luteinized granulosa cell tumors have shown an excessive estrogenic effect, i.e., cystic glandular hyperplasia.

The lipoids in arrhenoblastoma follow a definite pattern. The lipoid accumulation is practically wholly confined to the Leydig cells accompanying the mesenchymal masses, cords, or tubules. The lipoids in the four cases studied with the polarizing microscope were identified for the greater part as nonrefractile, with but a small amount of birefringent crystals showing oblique extinction. In contrast to this finding we mention the case report of Gnassi[12] who found that "double refractile crystals were conspicuous in the interstitial cells."

Hypernephromas of the ovary have been the subject of much controversy. These tumors, like the suprarenal cortical adenomas, may be virilizing in their effect. The presence of a great abundance of morphologically similar isotropic and anisotropic lipoids of similar staining reactions with Nile blue sulfate and sudan III in both the suprarenal cortical adenoma and the hypernephroma of the ovary studied by us permits of a more than casuistic inference.

Some significance, therefore, can be attributed to the lipoids in ovarian tumors. The deposition of lipoids in the incretory group resembles the deposition of lipoids in the normally functioning ovary, i.e., in the luteinization of theca cells, in the accumulation of lipoid droplets in the granulosa cells of the maturing Graafian follicle, and the corpus luteum; or the lipoid deposition may correspond to that observed in the male gonad after the fifth month of fetal life. It is assumed that in the normal gonad, both male and female, lipoid deposition is a process closely linked with endocrine metabolism and hormone storage. May it not be surmised that the lipoids in the incretory group of ovarian tumors are a part of a similar process?

CONCLUSIONS

Tissue sections from 32 solid ovarian neoplasms were studied with sudan III and Nile blue sulfate stains to ascertain the lipoid distribution. From this series, eight cases were selected to illustrate the specific and nonspecific distribution of the lipoids.

Fat stained sections were studied with the polarizing microscope, to ascertain to what degree refractile and nonfractile lipoids were present. The refractile lipoids were studied for their isotropic and anisotropic qualities, as well as for their axial and biaxial features.

Extraction and chemical analysis of the fat content in 11 of the tumors were done. Determinations were made on total lipoid material, total cholesterol, and lipoid phosphorus. It was found that the incretory tumors differed from the nonincretory tumors, in that the former have a consistently greater phospholipid and cholesterol content than the latter.

The chemistry of tumor cells is very much like that of the normal cells from which they arise, particularly in regard to their lipoid storage and chemical metabolism. The application of this principle may prove of value in determining an acceptable classification of the ovarian neoplasms.

The authors gratefully acknowledge their indebtedness to Edgar R. Pund, Augusta, Ga., for kindly advice and assistance rendered during the execution of this work and to Walter Schiller for permission to use his sections of arrhenoblastoma. We wish to thank Otto Saphir, Chicago; Charles Geschicter, Baltimore; Joseph Riopelle, Montreal; J. Pritchard, Montreal; J. M. Neely, Lincoln, Neb.; M. J. Schlesinger, Boston, for sections of tissue, some of which were of extreme usefulness in this study, also to the Spencer Lens Co. for the petroscope employed.

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DAILY GONADOTROPIC HORMONE TESTS DURING FIFTY COMPLETE MENSTRUAL CYCLES*

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THE development in civilized man of a greater sense of responsibility toward the consequences of his sexual encounters has led to a demand for information which could be used in controlling such consequences. Since the survival period of egg and sperm is short, the time relationship between ovulation and the sex act is immediately apparent as a determining factor and the importance of knowing at what time during the menstrual cycle ovulation occurs is therefore obvious.

Many techniques have been used. Hartman, in his excellent volume, *Time of Ovulation in Women*,[1] describes these methods and evaluates the results. Although not considering the question definitely answered, he finds the evidence from all sources sufficiently confirmatory to justify the statement:

> "On the whole the best evidence points to a midinterval ovulation as the rule for the human species. As the more objective and reliable proofs accumulate, they show a trend decidedly toward a complete denial of ovulation in the last quarter of the cycle, i.e., toward the establishment of the Knaus-Ogino law. But thus far we cannot yet give this final approval. We still have a long way to go before we can brand as a falsehood a woman's assertion that she conceived in the so-called sterile period of the cycle. There is still insufficient data for any actuarial expert to base the cost of insurance that might be sold with a book advocating the safe period.
>
> "Nevertheless, the opponents of the safe period are more and more placed on the defensive as new facts accumulate."

We may accept the view, then, that ovulation in women occurs usually during the midinterval of the menstrual cycle. If, however, the question be altered to read: "Does ovulation occur *only* during the midinterval?" we do not find the evidence for an affirmative answer nearly as complete. Since the publications of Knaus and Ogino appeared, in which the principle of midinterval ovulation was most strongly established, many investigators have devoted their attention mainly to this portion of the cycle and have neglected the earlier and later parts. This is particularly true where the direct method, that of ovarian inspection at laparotomy, has been used. And a rather imposing number of workers (Stein and Cohen[2] cite ten) have expressed the view that extracyclic ovulation may occur, either spontaneously or as a result of coitus. In other words, while a mass of data support the view that ovulation *usually* occurs during the midinterval, there is no such wealth of evidence that it occurs *only* at that time.

In the present study we attempted to obtain information concerning the time of ovulation by testing the day-by-day urine excretion for gon-

*This investigation was supported in part by a grant from the Penrose Fund of the American Philosophical Society.

adotropic hormone during 50 complete menstrual cycles. Not nearly enough data have been obtained to justify any far-reaching conclusions, but we are convinced that at least the possibility of several ovulations occurring per cycle has been established. If this possibility is to be taken into account, future studies will have to be so conducted that every day of the cycle is considered of equal importance. For such studies the method of urinalysis seems best suited as no method can be used which makes too great demands upon the forbearance of the subject. Daily uterine biopsies, uterine motility tests, withdrawal of blood, to say nothing of laparotomies, are clearly out of the question. Whether a positive test for gonadotropic hormone indicates that ovulation is impending or has occurred will be discussed later.

Experimental.—Kurzrok[3] in 1934 reported a study in which the method of testing the urine for gonadotropic hormone was used. This method is a modified Aschheim-Zondek pregnancy test[4] in which an alcoholic precipitate from 66 c.c. of urine is injected into a mouse. We have carried out preliminary studies in which this method was employed except that rats were used. (Herein may lie the reason for our failure to duplicate Kurzrok's results, as the mouse may be a more sensitive animal. This is true of the gonadotropic substance in menopause urine, which our substance resembles. Vide infra.) In any case, three complete cycles were tested by this method, no positive reactions occurred; the amount of urine was then doubled, eleven cycles being tested, a few scattered positives appeared. The amount was then increased to 240 c.c. The precipitates from this amount of urine were frequently toxic and although three more cycles were tested no positive reactions were obtained. The method of Katzman and Doisy[5] was then employed on 13 cycles. Again a few positive reactions were found but many of the animals died, making the study incomplete. None of these cycles is included in the present report.

The method next adopted and which proved very satisfactory, was that of Levin and Tyndale,[6] in which tannic acid is used as the precipitating agent. Either twelve-hour nocturnal specimens or full twenty-four-hour samples were collected, the active principle obtained by precipitation and, in the case of twelve-hour samples the entire precipitate, in case of twenty-four-hour samples one-half the precipitate, injected into a twenty-six-day-old female rat. Injections were made daily for three days and the animals sacrificed at the end of one hundred hours. A test was considered to be positive if the weight of the ovaries was double that of those in control animals. As a matter of fact, there were very few cases where any doubt existed as to whether a reaction was positive or not, the average weight of the ovaries of positively reacting animals being 52.2 mg. while that of 253 control animals was only 10.7 mg. Usually a series of animals would be examined showing no evidence of ovarian stimulation whatever. The next animal would show a gaping vagina, heavy estrus smear, enlarged uterus and ovaries hyperemic, greatly enlarged and mulberry-like in appearance. Sometimes this reaction was still present in the following animal, usually, however, it lasted only one day and again a series of completely negative animals would be encountered. Nearly all positive ovaries were sectioned and studied microscopically. The precipitate was remarkably nontoxic although in a few cases an animal died. We were fortunate that in these rare cases one animal of the pair survived and each day of the cycles presented is represented by at least one, usually by two, animals. Toxic effects were noted only during the warm months. It is a weakness inherent in this study that the number of animals per test is not greater. However, after the discouraging results obtained using smaller amounts of urine, we believed that the concentration of gonadotropic substance was in no case very great and that it would be better to use large doses and obtain unequivocal positive reactions when they did appear than to distribute the material among a larger number of animals. At present we are using the uterine weight method of Levin and Tyndale.[7] This method is apparently more sensitive and permits the use of larger numbers of animals. It may be mentioned, however, that the total number used in this study, including the preliminary studies, exceeded 4,000.

RESULTS

The results are presented in Charts 1 and 2 and are summarized in Table I. We desired to take into account variations among individuals, and variations from month to month in the same individual. Five of the 12 subjects were therefore tested through from six to eleven consecutive

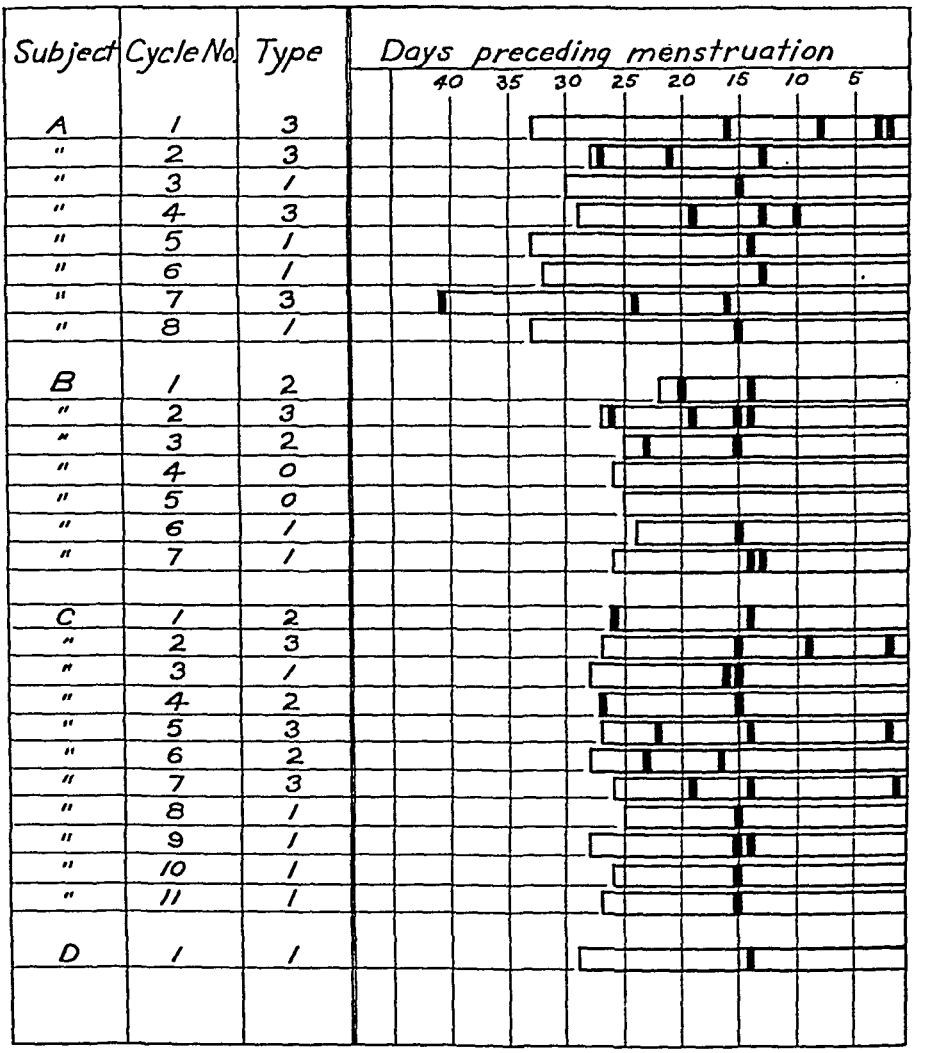


Chart 1.

Charts 1 and 2.—The blocks signify positive tests for gonadotropic substance. The different types are summarized in Table I.

TABLE I. CLASSIFICATION OF CYCLES

DESIGNATION ON GRAPH	DESCRIPTION OF CYCLE	NUMBER OCCURRING	PER CENT OF TOTAL
0	No positives at all	3	6
1	One positive, falling between days 16 to 13	21	42
1 a	One positive, falling on day 19 or 20	2	4
2	Two positives, with 6 to 12 days' interval between	13	26
2 a	Two positives, very close together	2	4
3	Three positives, at fairly regular intervals	9	18

cycles. These women were for the most part university students and their faithful cooperation in saving twenty-four-hour urine specimens (a decidedly inconvenient and occasionally embarrassing task) is greatly appreciated by the authors. A brief statement concerning each of the

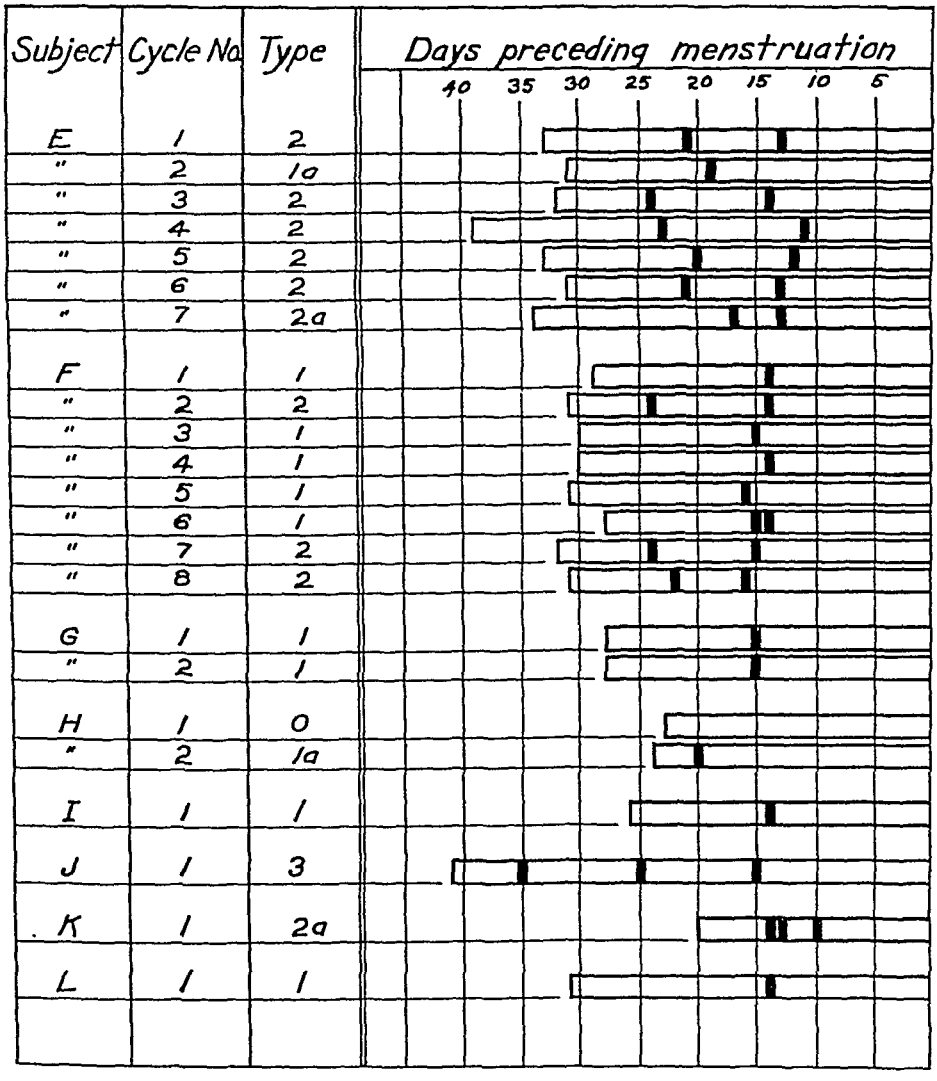


Chart 2.

subjects studied over long periods follows; the ages of the other subjects varied from 19 to 30, all were single with normal gynecologic histories.

Subject A. Aged 25, single, gynecologic history normal.
Subject B. Aged 36, single. Menses painful and protracted, condition later diagnosed as endometriosis.
Subject C. Aged 39, married, mother of three, gynecologic history normal.
Subject E. Aged 20, single, gynecologic history normal.
Subject F. Aged 20, single, gynecologic history normal.

It is at once apparent that positive reactions appear with far greater frequency than would be expected and that no type of cycle can be considered characteristic for a given subject. The classification into types is made only for the purpose of summarizing the results obtained in this study. The number of cycles, in view of the great variation shown, is

not nearly large enough to justify the conclusion that all cycles would fall into these groups nor that these percentages would hold for all women.

Histologic Results.—As stated, most of the positively reacting ovaries were studied microscopically. Again, larger numbers of animals should have been used in order to take into account individual differences among animals. This, for the reasons mentioned, was impossible. In general, it can be said that this substance is primarily follicle stimulating in its effect, however, varying degrees of luteinization had occurred in the heavier ovaries. No great difference in this respect could be noted between the positives found during the midinterval and those occurring at other times. Thus, so far as the effect produced on the rat ovary is concerned, there is no qualitative difference in the hormone produced at different times during the menstrual cycle.

Nature of the Gonadotropic Substance.—Comparative studies have been carried out on the gonadotropic substance contained in normal urine, prolan (from pregnancy urine), the gonadotropic substance in menopause urine and anterior lobe extracts. These results will be published elsewhere but may be summarized here. So far as its action upon increase in weight of ovaries and corpus luteum formation is concerned as well as its action upon the testes and seminal vesicles of immature males, the substance in normal urine seems closely related to, if not identical with, that present in menopause urine. The latter is believed by many investigators (Van Dyke,[8] pages 228 and 229) to be the true follicle-stimulating hormone of the anterior pituitary, with which belief our studies are in agreement.

DISCUSSION

The most important question in connection with this study is whether the sudden appearance of a high concentration of a substance which is capable of stimulating ovarian development in immature rodents signifies that ovulation in the human producing it is either impending or has occurred. It must be admitted at once that no such proof exists. However, the same doubt must prevail as to all indirect methods. Even inspection of the ovaries at laparotomy does not yield absolutely definite information. In fact, Hartman,[1] questions whether any observer is qualified to judge the age of a ripening follicle accurately enough to predict when it will rupture or to state with assurance how old a corpus luteum may be and thence deduce when ovulation had occurred. Of indirect methods whose use is practical over extended periods, the assay of the urine for gonadotropic substance seems to us the one which gives information most in harmony with present views concerning the control of ovulation. If any one view concerning ovarian control may be said to have gained universal acceptance it is the belief that this function is under hypophyseal control. There is no good evidence for species differences in respect to hypophyseal hormones, in other words, a substance which stimulates the ovaries of the immature rat would, presumably at least, stimulate the human ovary. Further, so far as our studies go, the urinary product possesses properties similar to, if not identical with, those of the anterior pituitary hormone itself, and, again presumably, may be considered as originating there.

On the assumption that the sudden appearance of a high concentration of gonadotropic substance in the urine indicates ovulation, examination of the data indicates that this occurred once during the cycle in 23 cases (46 per cent); twice in 15 cycles (30 per cent); three times in 9

cycles (18 per cent); and not at all in 3 cycles (6 per cent). These last may be interpreted as representing anovulatory cycles, the existence of which, in the monkey, is certain, and in the human being probable.

There are reasons for believing that ovulation may occur more than once per cycle. Of perhaps least importance, but not to be completely disregarded, is the frequent failure of conscientious effort on the part of intelligent women to control conception by means of the so-called safe period technique. Many of these failures may be due to errors in calculation, resulting from irregularities in the length of the menstrual cycle, but others may well be due to extraovulations.

A paper has recently appeared by Samuels[9] in which the time of ovulation was determined by means of the cycloscope. (This is a device which permits determination of the time of oxyhemoglobin reduction spectroscopically.) The author concludes that mature women always ovulate twice per cycle, young women three times. Here, as in all cases of indirect determination, doubt must exist as to the certainty of relation between the observed phenomenon and ovulation. However, Samuels has in some cases verified the result obtained spectroscopically by examination at laparotomy.

Certain other studies are suggestive in this connection. Gustavson and others[10] have reported on the excretion of estrin during the menstrual cycle. In this study we found that estrin excretion occurred typically in two peaks, the first being considered as related to follicular maturation and the second as due to corpus luteum activity. These peaks might be explained on a different basis, namely as two successive follicular maturations (perhaps in both cases followed by ovulation) during the same menstrual cycle. We are at present investigating this relationship by assaying the same urines for both the gonadotropic principle and for estrin.

A final point may be made for the case of multiple ovulation on the basis of the data presented. If one includes days 16 to 13 as representing the midinterval, 41 of our cycles (82 per cent) show a positive reaction at that time. If one broadens the midinterval to include days 20 to 11, 47 cycles (94 per cent) are positive. If one includes only the positive cycles, the incidence is 100 per cent. This conforms with the evidence from other sources and strengthens the view that the positive response indicates ovulation. But if that be true, one is almost forced to assume that positive reactions at other times indicate the same thing. As was pointed out previously, the response at other times was just as strong quantitatively, as indicated by ovarian weights, and of the same nature qualitatively, as indicated by histologic study, as that obtained during the midinterval. The explanation may be, though this is speculation, that the ovarian cycle and hypophyseal cycle are independent, and the gonadotropic hormone will only produce ovulation if the ovary is in proper phase with it.

As concerns the use of such a test as this in the diagnosis of sterility of hypophyseal origin, one is perhaps on safer ground. Barring the complication of an occasional anovulatory cycle in the normal female, if day by day tests over a period of several cycles were consistently negative the diagnosis of sterility due to failure of the hypophysis to stimulate the ovary would be justified. This would indicate as well that the treatment should consist of gonadotropic rather than estrogenic hormones. However, prolan would certainly not be indicated, as the effect desired is a follicle-stimulating, not a luteinizing, one. Until potent

gland extracts are available, efforts to prepare a potent gonadotropic preparation from menopause urine (or pregnant mare serum) would be worth while, as these substances appear to have the same properties as the gonadotropic substance produced by the normal female during the menstrual cycle.

SUMMARY

1. Day by day tests of the urine for gonadotropic hormone were made during 50 complete menstrual cycles. The tannic acid precipitation method was used. Positive responses were found as follows: (a) During 3 cycles, no positive response. (b) During 21 cycles, one positive response, falling between days 16 to 13. (c) During 2 cycles, one positive response, falling on day 19 or 20. (d) During 13 cycles, two positive responses, with a 6- to 12-day interval between. (e) During 2 cycles, two responses, falling very close together. (f) During 9 cycles, three responses at fairly regular intervals.

2. The bearing of these findings upon the question of the time of ovulation is discussed. The only conclusion that can be drawn is that either ovulation frequently occurs more than once during the menstrual cycle or else that ovulation is not directly dependent upon hypophyseal stimulation. In either case, the reproductive cycle in the human female is apparently a more complex and variable phenomenon than is usually supposed.

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Latzka, A.: A Positive Aschheim-Zondek Reaction in Tuberculous Disease of Uterine Tubes, Zentralbl. f. Gynäk. 61: 277, 1937.

The writer discusses various conditions other than pregnancy that cause increase of gonadotropic output in the urine. Among others he mentions tuberculous disease of the uterine tube referring to an observation reported by Wilson. Latzka corroborates Wilson's finding by describing two personal observations. He mentions a case of threatening abortion as result of tubal adhesion. A positive Aschheim-Zondek case readily leads to the incorrect diagnosis of extrauterine pregnancy, definite differentiation being possible only by means of a laparotomy.

J. P. Greenhill.

THE ETIOLOGY AND TREATMENT OF ENDOCERVICITIS AND CERVICAL EROSIONS*

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ENDOCERVICITIS is not a sharply defined clinical or histologic entity. An excessive amount of cervical discharge, with or without erosion, is clinically regarded as evidence of endocervicitis, but since the normal cervical mucosa contains mucus-secreting glands, a certain amount of discharge is physiologic, and it is difficult to draw a dividing line between a normal and a pathologic amount of secretion. A definite diagnosis is possible in those cases in which the cervical discharge is associated with a reddened area around the external os, the so-called erosion. It is generally believed that an erosion does not exist without endocervicitis, from which it originates. Histologically, the diagnosis of a simple endocervicitis without erosion is based on the presence of hyperplasia and hypersecretion of the glandular elements. In many cases inflammatory changes in the stroma are inconspicuous or entirely absent, the prominent microscopic feature being the preponderance and hyperactivity of the columnar cells. Marked mitotic activity, with crowding and desquamation of the columnar cells, is considered as the manifestations of an inflammatory process. The histogenesis of erosions has long been the subject of controversy and a voluminous literature is available on this subject. Erosion, histologically, is not what the term implies, the protective epithelium not being really lost. The red area, which resembles a denuded surface, is covered with a single layer of columnar epithelium. By what mechanism the squamous epithelium of the portio disappears, to be replaced by columnar cells, is unknown. The generally accepted view is that the irritating hypersecretion macerates the squamous epithelium, which results in a denudation around the external os. This denudation exists for only a short time, the columnar epithelium of the endocervix proliferating rapidly over the raw area. It has been contended that this alteration is due to the fact that columnar epithelium is more resistant to maceration than is squamous epithelium. Infection is regarded as the causative factor behind these histologic changes. The invasion of the cervical glands by bacteria produces hyperemia, which eventually leads to hyperplasia and hypersecretion.

The histologic interpretation of endocervicitis and erosion, and the etiologic deductions therefrom, are based on the assumption that the cervical mucosa maintains a constant histologic structure, in which cyclic transformations due to ovarian hormone influence do not occur. In previous papers I have reported my observations, which demonstrated menstrual cyclical changes in the cervical mucosa and their correlation

*Read at a meeting of the Brooklyn Gynecological Society, December 2, 1938.

with ovarian hormonal activity. I also pointed out that various phases of the histologic cycle of the endocervix may be erroneously interpreted as inflammatory reaction. It is evident that the etiologic and histologic conceptions of endocervicitis and erosion were formulated on a basis which my previous studies seemingly controverted. The hormonal influence on the cervical mucosa is such an important factor in this structure's physiologic activity that a proper evaluation of the histologic findings does not seem possible without a knowledge and full appreciation of the effects of the ovarian hormones. If this premise is correct, it would seem logical to predict a revision of some of the previously held views concerning cervical erosion and endocervicitis.

To demonstrate the influence of the ovarian hormones on the cellular structure of the endocervix, I have carried out some experimental studies on six women whose cervical mucosa was subjected to the atrophic changes incidental to castration or the physiologic menopause.

Of the 6 patients selected, 3 were castrated surgically because of bilateral tubo-ovarian disease, and 3 were undergoing a natural menopause. These 6 women were divided into 3 pairs. Those in Group I were given estrin exclusively, in Group II progestin only, and those in Group III were treated with both estrin and progestin. In each instance a cervical biopsy was taken before beginning hormonal treatment, and the histologic picture was similar in all 6 cases. The stroma as well as the glandular structure undergoes characteristic changes after the cessation of menstruation. The stroma becomes dense connective tissue, and the cells are small, pyknotic. The blood vessels have unusually thick muscular walls. The glands are regular in outline, round or oval shaped, with collapsed lumina. The lining epithelium in some of the glands is completely cast off, whereas in others the columnar cell lining reveals signs of pyknosis. Inactivity and gradual disappearance of the columnar cell elements are the outstanding features of the menopausal cervical mucosa. I observed that after surgical castration these atrophic changes progress rapidly, whereas in the physiologic menopause this alteration is more gradual. This seems to indicate that ovarian hormone production may continue for a long time after the clinical onset of the menopause.

Another cervical specimen was taken after the completion of the hormonal treatment, and the two specimens in each case were subjected to a painstaking comparative histologic study. The history and photomicrographs of one case in each group are detailed herewith.

CASE 1.—A 41-year-old woman, married nineteen years, had one miscarriage twelve years previously, but no other pregnancies. Menstrual history normal. She presented herself complaining of a profuse yellowish bloody discharge of two weeks' duration, with severe abdominal pain in the left lower quadrant, backache, and frequent, painful urination. Gynecologic examination revealed a profuse discharge from the cervical canal, tinged with blood. The portio appeared normal. The corpus was enlarged, firm, and in good position. On the left side a large, tender tubo-ovarian mass which extended back to the cul-de-sac was palpable. The right adnexa could not be felt. The diagnosis of a left tubo-ovarian abscess was made. Operative findings confirmed the diagnosis, with the addition of diseased adnexa on the right side. A bilateral salpingo-oophorectomy was done with conservation of the uterus, and the patient made an uneventful recovery.

Eight weeks after the operation, examination of the patient revealed a small, atrophic portio, complete lack of discharge, a small uterine corpus, and a free pelvis. Before the institution of hormonal treatment a cervical biopsy was taken, the histologic study of which revealed the following: The surface was covered with a single layer of columnar epithelium with pyknotic, deeply stained nuclei. Some of the glands, which were oval or round in shape, had regular outlines and were lined with columnar epithelium similar to that found on the surface. These glands had collapsed lumina and did not reveal any signs of secretion. In the majority of the glands an extensive desquamation of the lining membranes was noted. The stroma



Fig. 1.—Atrophic cervical mucosa in Case 1.

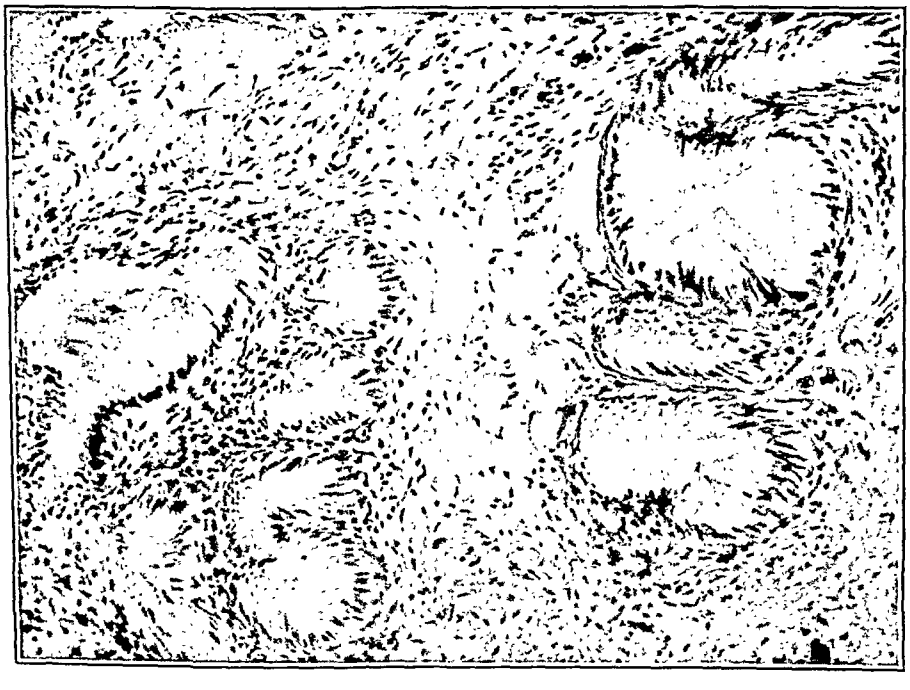


Fig. 2.—Cervical mucosa in Case 1 after the administration of 48,000 rat units of progynon B.

was a dense connective tissue with a conspicuous number of thick-walled, contracted blood vessels. Fig. 1 illustrates a typical area of this specimen under low power.

The patient received hormonal treatment over a period of six weeks. All together 48,000 rat units of progynon B were given intramuscularly. After the last injection another cervical specimen was obtained, which revealed the following picture: The surface of the mucosa showed extensive folding, imitating papillae. The epithelium was of a high columnar type; the nuclei were pale and swollen, migrating toward the center of the cells. A conspicuous number of mitoses could be seen. The glands were numerically increased, and markedly distended and branched. The lining epithelium of the glands was high columnar, with increased cytoplasm, which narrowed the glandular lumina. The nuclei were pale, approaching the center of the cells and leaving in many places a lucid zone between them and the basis. The stroma cells had swollen nuclei, and the connective tissue fibers were separated by marked edema. The blood vessels were distended by erythrocytes and a few white cells (Fig. 2).

This case demonstrates the change of an atrophic cervical mucosa into a highly active structure following the administration of large doses of estrin. In some places the typical, picture of a glandular hyperplasia was produced, similar to that found in cases of endocervicitis. The structure of the glands resembled the one usually found in the late proliferative menstrual phase. The histologic transformation of a dense, ischemic connective tissue into an edematous and hyperemic structure simulates an inflammatory condition. In the course of the treatment changes were noted in the gross appearance of the cervix. The small, firm anemic and dry portio gradually changed into a larger, soft, pink-colored structure. After the administration of 10,000 R.U. of progynon B, a scant discharge appeared from the cervical canal, which was noticeable throughout the period of treatment.

The other case in this group was that of a woman who was surgically castrated for bilateral cystic disease of the ovaries. The first cervical specimen taken ten weeks after the operation showed an identical histologic picture as in the first specimen in the case just described. This patient was given 15,000 R.U. of progynon B by intramuscular injections over a period of three weeks. The cervical specimen taken after the completion of the treatment revealed a moderate increase in the number of the glands. The glands were of irregular outline, profusely branched, and the lining epithelium was of a high columnar type, with pale, spindle-shaped nuclei. Changes in the stroma were inconspicuous. Notwithstanding the relatively small dose of estrin, a reactivation of the atrophic cervical mucosa was evident in this case.

Two patients of the second group were treated exclusively with progestin, and one case is described in detail.

CASE 2.—A fifty-seven-year-old woman, had two children thirty-five and thirty-four years previously. Seventeen years before, she had a right salpingo-oophorectomy for ectopic pregnancy. The menopause had been established ten years ago. Gynecologic examination revealed a small atrophic cervix, free from discharge, a small freely movable corpus, and the adnexa were not palpable. A cervical specimen was taken which showed the following histologic picture: The covering epithelium was partly low columnar, partly cuboidal, with deeply stained small nuclei arranged near the base. The glands were few with narrow, collapsed lumina; some were lined with low columnar epithelia, the nuclei being markedly pyknotic and basally arranged, while other glands revealed the lining epithelium in the process of desquamation. The stroma was dense connective tissue, the cells having small deeply stained nuclei. The blood vessels were contracted and had thick muscular walls. A squamous epithelial covering could be seen over a small area, showing several layers, chiefly consisting of prickle cells, and gradually decreasing to a thin layer (Fig. 3).

This patient received 60 mg. of proluton by intramuscular injections over a period of four weeks. No clinical change in the appearance of the portio was noted. After the last injection of proluton another cervical specimen was obtained and histologically examined. The glandular elements and the stroma showed a substantially identical picture with that found in the first specimen, but a marked change was noted in the histologic appearance of the squamous epithelium. An active proliferation was conspicuous, the squamous cells invading the cervical canal,

Approximately three-fourths of the length of the canal was covered with a high layer of noncornifying stratified epithelium, with complete disappearance of the columnar type. Numerous mitotic figures could be seen in the squamous epithelial layer. Fig. 4 visualizes the epithelial covering of the mucosa within the cervical canal.



Fig. 3.—Atrophic squamous epithelium in Case 2.

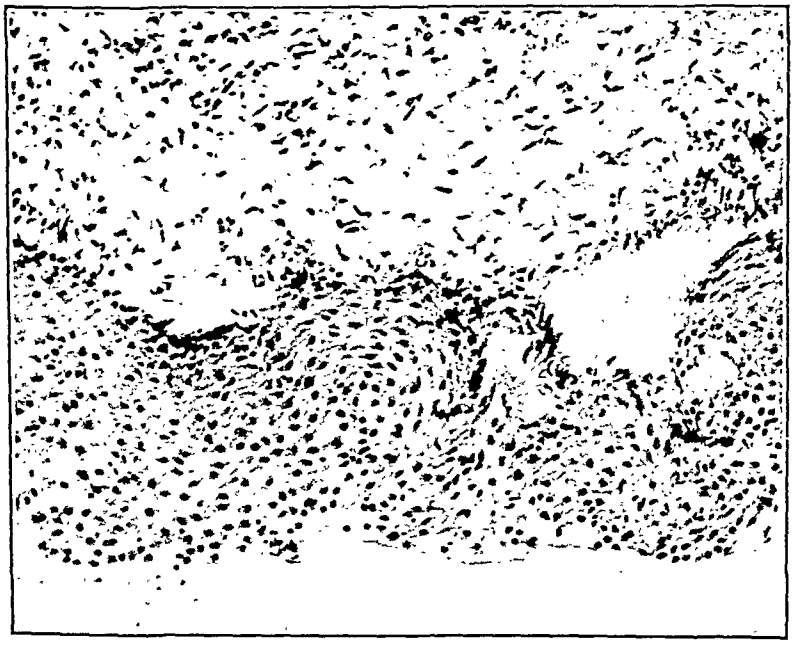


Fig. 4.—Squamous epithelium in Case 2 after the administration of proluton.

This case, in which a woman in the menopause was treated with progestin, does not reveal any appreciable histologic changes in the glandular structure or the stroma of the atrophic cervical mucosa. A marked stimulation of the squamous epithelial elements was effected, however, with resulting invasion of the endocervical surface.

In the third group, consisting of two menopausal patients, large doses of estrin and progestin were administered simultaneously. The following case report and photomicrographs demonstrate the results obtained.

CASE 3.—A 52-year-old woman, never pregnant, had always menstruated regularly until five years ago, when the menopause occurred. Gynecologic examination revealed small, atrophic genital organs. The patient complained of menopausal symptoms. A cervical specimen was taken, which showed the following picture: The surface was covered with low columnar epithelium, having little cytoplasm and deeply stained pyknotic nuclei arranged near the base. The glands were relatively numerous, but were small and symmetrically round. The lining epithelium was low columnar in some places, in others cuboidal with very little cytoplasm and deeply

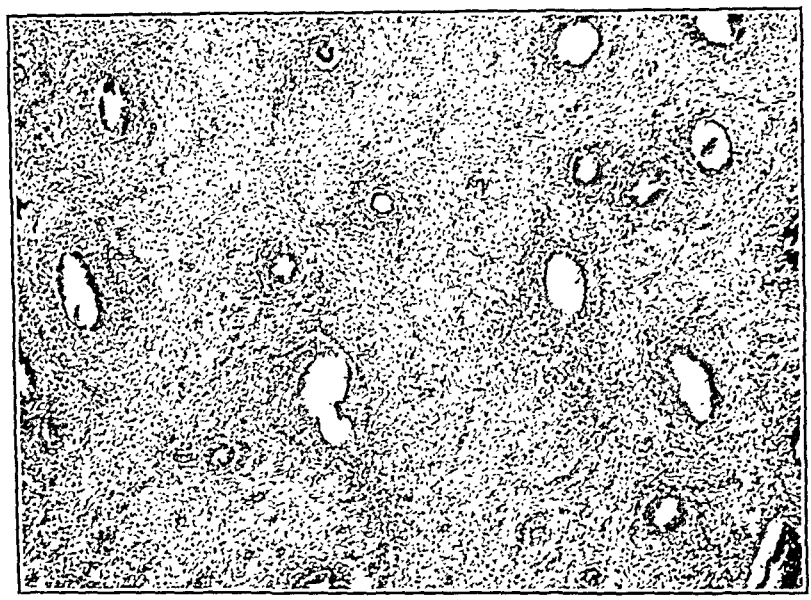


Fig. 5.—Atrophic cervical mucosa in Case 3.

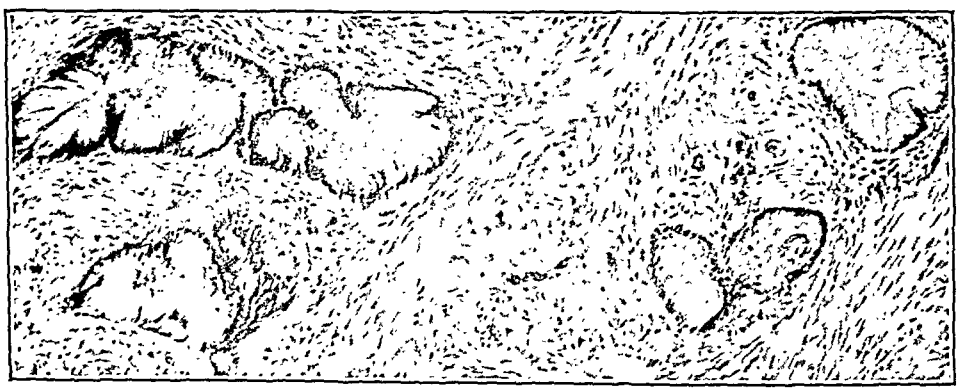


Fig. 6.—Cervical mucosa in Case 3 after simultaneous administration of progynon B and proluton.

stained small nuclei. In many glands the lining epithelium was completely or partially desquamated. The stroma was dense connective tissue, the blood vessels were contracted and had thick muscular walls. Squamous cells could not be found in any part of this specimen (Fig. 5).

The patient was treated with ovarian hormones over a period of four weeks. She received 50,000 rat units of progynon B and 35 mg. of proluton intramuscularly, and began to menstruate after the completion of this treatment, having a normal flow for five days. The cervical specimen obtained after the last hormonal injection was subjected to careful study and revealed the following: The glands were not noticeably increased in number, but revealed marked structural changes. Their shapes were irregular, with numerous projections into the surround-

ing stroma. The lining epithelia were of the high columnar type with pseudo-projections into the lumina. The nuclei were elongated, pale, and the cytoplasm was increased. The stroma had a loose texture; a few capillaries and some scattered round cells were seen (Fig. 6). An area of the surface was found to be covered with a very high layer of stratified epithelium. The basal layer of this epithelium showed irregular projections into the underlying stroma. The cells in the upper



Fig. 7.—Marked hyperplasia of the squamous epithelium in Case 3 after administration of progynon B and proluton.

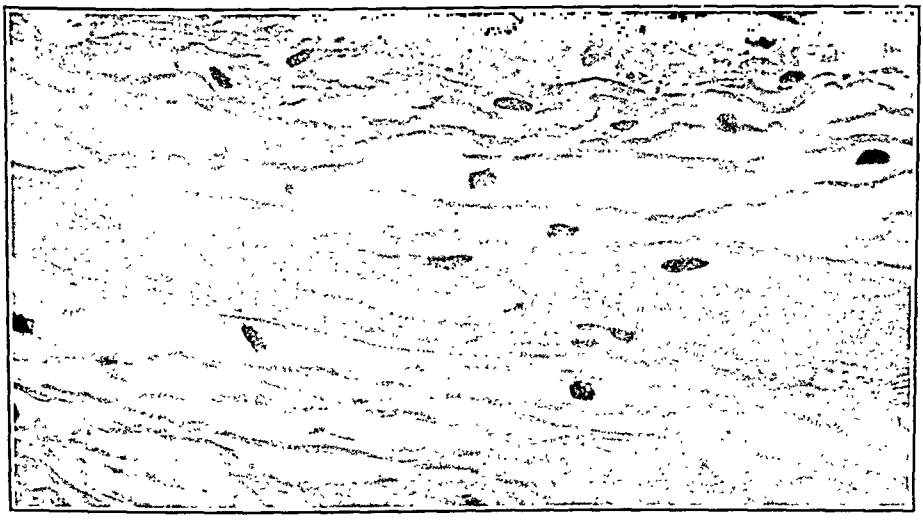


Fig. 8.—*Parakeratosis in Case 3.*

layers revealed vacuolization. In one small area, approximately 1 mm. below the basal layer, an epithelial island could be seen in the stroma, which was well demarcated and contained deeply stained regular epithelial cells. Fig. 7 illustrates the squamous epithelial picture in this case. A portion of the squamous epithelium revealed the typical picture of parakeratosis (Fig. 8).

The simultaneous administration of estrin and progestin produced in this menopausal patient a distinctly different histologic picture in the cervical mucosa from

that observed in similar cases treated exclusively with estrin or progestin alone. The reactivation of the atrophic cervical mucosa was as striking in this instance as in the other cases, but it seems that the simultaneous action of estrin and progestin altered the respective histologic effects of these two hormones. Notwithstanding the same dosage of estrin as in Case 1, the glandular hyperplasia and the hyperemia and edema of the stroma failed to develop. The proliferative activity of the columnar cell elements seemed to be depressed, probably due to the inhibitory influence of progestin. The squamous epithelial changes in this case deserve special comment. The marked hyperplasia resembles the embryonic type of epithelium. The histologic significance of this, and that of parakeratosis, found in another portion of the specimen, is not definitely known. Parakeratosis is an incomplete cornification of the epithelium. Schiller devoted careful attention to this condition, and believes that the portio-epithelium always possesses a latent potency for prosoplastic cornification. The stimulus which awakens this latency may be external, such as pressure, dryness, or chronic inflammation and syphilis. There are cases, however, in which para- and hyperkeratosis develop without any known external or internal stimuli, which are the spontaneous types. My observation in this case seems to indicate that prosoplastic changes of the portio-epithelium may be produced by a dysfunction of the ovarian hormones.

Summing up my observations in 6 cases, in which the histologic effects of the ovarian hormones were studied on the atrophic cervical mucosa, the following conclusions seem justified. Constant changes occurred which prove the ovarian hormonal participation in the histologic transformations of the cervical mucosa. Alterations resembling inflammatory conditions were produced by the administration of hormones. Specifically, estrin seems to stimulate the proliferation of the columnar cell elements, with hyperemic and edematous changes in the stroma. The administration of large doses of estrin changed the atrophic cervical mucosa into a structure which showed the typical picture of glandular hyperplasia with marked hyperemia, a condition commonly found in endocervicitis cases. Progestin, on the other hand, seemed to stimulate the growth of the squamous epithelial elements. The invasion of the endocervical surface by this epithelium was pronounced after the administration of progestin. There is suggestive evidence that the combined action of estrin and progestin alters the specific histologic effects of the individual hormones. Progestin seems to exert a certain inhibitory effect on the estrin action, while estrin seems to accentuate the progestin's stimulating effect on the squamous epithelium.

Endocervicitis and erosion are chiefly characterized by an active proliferation of the columnar epithelium, deep in the stroma in the form of a glandular hyperplasia, and on the surface by considerable folding of the covering columnar layer and invasion of the portio surface. According to my observations such histologic changes may be produced by an unopposed estrin action. Should this etiologic consideration be true, the inhibitory effect of the progestin may be used for practical purposes, in bringing about a control of the pathologically active estrin function. To ascertain whether histologic pictures in the cervical mucosa, regarded as endocervicitis, can be influenced by the administration of progestin, further studies were carried out. Three nulliparous patients between the ages of 25 and 34 were selected. They all had a profuse cervical discharge with marked erosions, but otherwise were normal. Cervical specimens were taken from all three and showed

identical histologic pictures. Treatment with progestin was begun and continued for two months in each case. After completion of the treatment another cervical specimen was taken on exactly the same day of the intermenstrual period as the first one. The two specimens in each case were subjected to a comparative study, with the same results in all three cases. The following case and photomicrographs are typical.

CASE 4.—A 31-year-old woman, married for eight years, never pregnant. Menstruates profusely every twenty-six or twenty-eight days, lasting seven to eight days. Patient's chief complaints were: Menorrhagia and profuse white discharge. There was a marked erosion around the external os, with a profuse yellowish discharge from the cervical canal. The uterus was slightly enlarged, firm, freely movable, and the adnexa were negative. The first cervical specimen was obtained on the sixteenth day after the day of onset of her previous menstruation. Histologic study revealed the following: The surface was covered with high columnar epithelium. The



Fig. 9.—Glandular hyperplasia in Case 4.

nuclei were near the basal membrane and were deeply stained. The glands were closely packed, with papillary projections into the lumen due to the folding of the lining epithelium. The columnar epithelial lining of the glands consisted of very high cells with much cytoplasm; the nuclei were relatively small, situated near the basal membrane; many cells were markedly swollen and among these some were of the basket cell type. The stroma was markedly edematous, a few arterioles had their lumina filled with erythrocytes and a few white cells. Fig. 9 represents this specimen, showing the characteristic picture of a glandular hyperplasia in the early secretory phase.

The patient received in all 45 mg. of proluton by intramuscular injections over a period of two months. Its clinical effect was a change in the menstrual bleeding. While menstruation appeared at the expected time, the first period after beginning treatment was only of five days' duration with a moderate flow, and the second one thereafter lasted only four days with scanty bleeding. The usual symptoms of discomfort during the first two days of menstruation were entirely absent. After the proluton therapy a second cervical specimen was taken again on the sixteenth day following the first day of the bleeding. The histologic picture of this specimen shows the surface covered with partially low, partially cuboidal columnar epithelium.

The swollen nuclei are pale everywhere and do not reach the basal membrane. Few of them reveal migration toward the center of the cells, showing in such places a lucid zone between them and the basis. Indications of secretion are conspicuously absent. The stroma is dense and contains a few thick-walled arterioles and capillaries. These characteristics represent the proliferative phase of the menstrual cycle. Fig. 10 is a low power visualization of this picture.

In three cases of endocervicitis and erosion the administration of progestin produced marked histologic changes in the cervical mucosa. In all three a moderate decrease in the number of glands was noted, the hyperemic and edematous stroma changed into a dense structure, and apparently the persistent progestin action disturbed the normal course

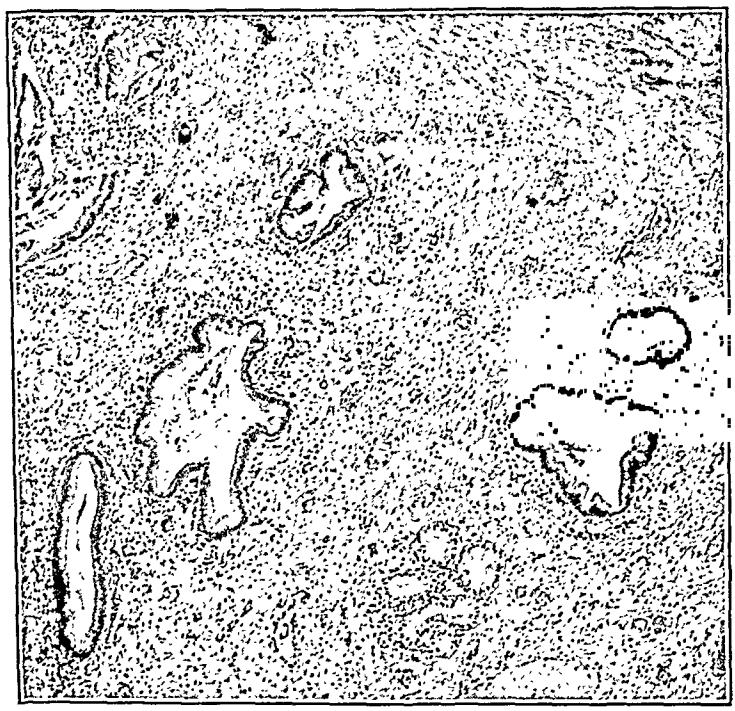


Fig. 10.—Cervical mucosa in Case 4 after the administration of proluton.

of the histologic cycle, since the secretory phase failed to develop at the expected time, the glands remaining in the proliferative stage. For the proper evaluation of these results it must be remembered that proluton was not given for therapeutic purposes. Small doses over a comparatively short period of time were administered only to ascertain whether the hormonal principles in the histologic interpretations of the cervical mucosa could be corroborated. Had infection been the etiologic factor in these cases, treatment with progestin would not have changed an inflammatory histologic picture in the cervical mucosa. The progestin effect in these cases not only proves indirectly that overproduction of estrin was responsible for the changes usually regarded as endocervicitis, but also intimates that the therapeutic problems involved in this condition may be approached on a hormonal basis.

DISCUSSION

Endocervicitis and erosion are generally believed to be the results of an inflammatory process due to infection. However, in the majority of

cases a specific infectious agent cannot be ascertained by clinical investigation. Furthermore, it is a recognized fact that the present histopathogenetic explanation of erosions cannot be verified by the histologic findings in many cases. The physiologic function of the two cervical epithelia, and its dependence on ovarian hormonal activity not having been recognized, histologic interpretations in the cervical mucosa have been made on a theoretical basis. According to my observations, ovarian hormone action is capable of producing histologic changes in the cervical mucosa, which have formerly been interpreted as inflammatory conditions. The possibility of a hormonal-cervical pathologic alteration makes the infectious-inflammatory etiology of endocervicitis and erosion problematical. In an attempt to determine the histogenesis of this pathology, the clinical and histologic manifestations of endocervicitis and erosion must be subjected to a critical survey.

The clinical occurrence of endocervicitis and erosion is not limited to any age-group, from the time of birth to the age of menopause.

Fischel investigated the portio of twenty-eight stillborn female infants, and found cervical erosion in 36 per cent of his cases. R. Meyer places the incidence of erosions in newborn infants at 33 per cent. No statistical data are available on the prevalence of erosions in young virgins, the inspection of the portio through an intact hymen not being practicable. Excessive cervical discharge in young girls, however, is not rare and observations in occasional cases, in which speculum examination can be carried out, indicate that clinical symptoms of endocervicitis and erosion are as frequent in this age group as they are in adults. Fulkerson studied 6,483 adult women and found an incidence of 33 per cent of endocervicitis.

After the menopause and after surgical removal of the ovaries, the incidence of this pathologic condition is distinctly less. The occurrence of endocervicitis and erosion in a fairly constant percentage from the time of birth to the age of menopause, and its disappearance after the cessation of ovarian activity do not seem to support the theory of an infectious etiology; on the contrary, it is suggestive of an interrelationship between hormonal action and the pathology.

Bacterial invasion of the cervical glands with resulting hyperemia and hypersecretion is supposed to be the cause of endocervicitis and erosion. Several investigators (Stroganoff, Menge, Curtis, etc.) have reported that bacteria are not normally found above the level of the external os. It remains problematical whether or not bacteria are able to pass through the external os, unless a predisposing hormonal factor is present. The most frequent source of female genital infection is the gonococcus. This specific agent is believed to play a prominent role in the production of endocervicitis. Kidd and Simpson investigated 223 cases of known gonorrheal infections and found erosions in 20 per cent of them. In 382 cases in which gonorrhea could be ruled out, erosions were found in 40 per cent. Consequently, erosion was found to be twice as frequent in nongonorrheal as in gonorrheal patients. This observation seems to prove that there is no causative correlationship between gonorrhea and erosion. Another possible source of female genital infection is incidental to labor. Traumatism of the cervix

during labor is presumed to facilitate invasion by bacteria, with subsequent inflammatory changes. This theory seems to be supported by the clinical observation that erosion is more frequently found in parous than in nonparous women. According to the estimation of various authors, the incidence of erosions is 80 per cent in parous as against 25 per cent in nulliparous women. These statistics imply that 55 per cent of all women who undergo labor are exposed to infection, with resulting permanent damage to the cervical structure. In the proper interpretation of these figures certain factors have to be taken into consideration. The fact is that a considerable number of women have their first gynecologic examination after childbirth. When evidences of endocervicitis and erosion are found at this time, there is a tendency to attribute them to birth trauma, although the condition may have been present for a long time before confinement. It may have passed unrecognized, since this pathology does not necessarily produce symptoms which would make a gynecologic consultation imperative. The establishment of a causal relationship between childbirth and erosion would be possible only if cervices were to be regularly inspected before and after confinement. Such a scrutiny of patients is rarely undertaken. Another important factor is the observation that erosion frequently makes its first appearance during the course of pregnancy. These so-called pregnancy erosions are rarely recognized, since speculum examination of pregnant women is not routinely made. Such erosions are definitely of noninfectious origin and may persist long after the confinement. Etiologically, their association with hyperfolliculinism of the ovaries, concomitant with pregnancy, is a reasonable hypothesis.

The clinical course of endocervicitis and erosion is unparalleled by any other inflammatory process in the genital tract, as these lesions are known to persist for many years, without any tendency toward spontaneous cure. Furthermore, they are highly resistant to the usual treatment of inflammatory conditions. In the course of several years, sudden exacerbations or recurrences may occur without any evidence of a new infection. The lack of recuperative power in the cervix is difficult to explain, since it is acknowledged that other parts of the genital lining membranes are capable of returning to normal within a relatively short period of time, even after profound structural changes. It has been contended that the cause of the cervical mucosa's different behavior in inflammatory processes can be explained by its unchangeable character. This theory is no longer tenable, since the histologic cycle in this structure has been demonstrated. Undoubtedly, irritative factors other than infection may account for this pathologic condition's persistency. The ever changing ovarian hormone action may account for the unstable appearance of erosions, and the failure of cure with antiseptic medications.

That erosion is not a localized process, strictly confined to the uterine cervix, is substantiated by several associated clinical symptoms. The size and consistency of the uterine corpus, as well as those of the cervix, are changed in these cases. Large uteri with hypertrophied cervices are

usually found associated with erosions, their consistency being soft, somewhat resembling an early pregnancy. The menstrual history usually discloses profuse and prolonged bleedings. Erosions do not occur in genital hypoplasias. All of these clinical manifestations are strongly suggestive of an ovarian participation in the pathology of erosion, involving to a certain degree the entire genital tract.

This short critical review of the clinical features of endocervicitis and erosion clearly demonstrates that there is no conclusive evidence to support the theory of an infectious origin, whereas an objective interpretation of the clinical symptoms strongly indicates an ovarian hormonal influence.

A scientific determination of the genesis of endocervicitis and erosion is possible only by an analytic histologic study of the cases. When the entire vaginal surface of the portio of the cervix is covered with squamous epithelium, it is considered to be normal. An extension of the columnar lining of the cervical canal to the outer surface of the portio constitutes the clinical picture of erosion. The histologic process whereby the replacement of the squamous epithelium by the columnar type is effected is not definitely known. The maceration theory assumes that the irritative action of the mucopurulent cervical discharge is responsible for the destruction of the squamous epithelium. Clinical observations prove, however, that many cases with profuse mucopurulent discharge from the cervical canal are seen without an erosion formation. It is evident, therefore, that discharge alone cannot explain the genesis of erosions. Furthermore, it is a known fact that histologically the squamous epithelium is a sturdy, resistant structure, much more so than the columnar epithelium. Nature provides squamous epithelial coverings on surfaces which are likely to be exposed to irritations. Histologic experience has shown that squamous epithelium reacts to chemical irritations not with loss of tissue, but with a protective proliferation. There is no evidence to indicate that the squamous epithelium of the portio is in any way biologically different from that found elsewhere. Considering all these facts, the active proliferation of the columnar cell elements with concomitant disappearance of the squamous epithelium cannot be explained satisfactorily on a maceration basis.

The outstanding histologic feature, uniformly found in all endocervicitis and erosion cases, is a pathologic preponderance of the columnar cell elements. Other histologic changes, such as hyperemia, edema, leucocytosis, desquamation, are present in some cases, and absent in others. I have demonstrated in previous papers and in the present experimental studies that all these histologic changes may be produced in the cervical mucosa by hormonal stimulation. Consequently, the histologic interpretation of these pictures should be made on the same basis as in the endometrium. Just as the terminology of endometritis was discarded, and replaced by hormonal dysfunction, endocervicitis should be re-evaluated on a hormonal basis.

In the hormonal explanation of the histogenesis of erosions, certain developmental facts have to be considered. In the intrauterine development of the fetus the entire genital tract is primarily lined with

columnar epithelium. This type of epithelium is gradually replaced by squamous epithelium in the vagina, the transformation beginning at the sinus urogenitalis. From there the squamous epithelium begins to grow upward into the vagina, until the level of the external os is reached. According to R. Meyer, in about one-third of the newborn infants, the upward growth of the squamous epithelium is arrested before the external os is reached, and these cases show the clinical picture of erosion. In another one-third, the demarcation line between the two epithelia is at the anatomic site of the external os. In the remaining third, the squamous epithelium grows upward beyond the external os; in these cases the junction of the two epithelia is found within the cervical canal. According to these observations, only in one-third of the cases do the two epithelia meet at the anatomic designation of the external os. Although the factor governing the relationship between the two epithelia is not known, R. Meyer expressed the view that probably ovarian factors are important influences. His view was supported by noting that after birth, the fetal uterus becomes markedly decreased in size. The emancipation of the infant from the maternal ovarian influences seems to be a logical explanation of this phenomenon. The results of my recent studies leave little doubt of the nature of the influences which regulate the equilibrium of the two epithelia in the cervix. Estrin has a stimulating effect on the growth of the columnar epithelium. The increased production of this hormone in pregnancy is bound to exert its influence on the fetus through the blood circulation. The differentiation of the two epithelia in the genital tract of the fetus begins when the independent function of the fetal ovaries is established. It is fair to assume that thereafter the extent to which the squamous epithelium is able to displace the columnar epithelium in the vagina and on the portio will depend on the individual hormonal capacity of the ovaries. Since the balance between the two ovarian hormones is unstable, the two epithelia are in a constant restless stage, and consequently, the line of demarcation is not permanent. It is not justifiable, therefore, to designate any fixed line in the genital tract as normal for the junction of the two cervical epithelia. In the pathologic evaluation of cervical erosions, this fact should be considered.

Erosions, notwithstanding their identical clinical appearances, are divided into two large groups: the congenital and the true. An exact histologic criterion by which a clear-cut differentiation between these two types can be established is not available. They both have in common a single layer of columnar epithelial covering on the surface of the portio, with marked increase of the glandular elements in the stroma. There are cases in both groups which reveal a complete lack of inflammatory changes; on the other hand, several congenital erosions have been found with signs of marked hyperemia. There is no way of determining in an adult whether a certain lesion is a persistent congenital or an acquired erosion. It must be remembered that a congenital erosion is certain to undergo histologic changes after the menstrual cycle becomes established. A misinterpretation of the effects of the

histologic cycle in the cervical mucosa may be responsible for a false differentiation between the two types of erosions.

The treatment of endocervicitis and erosion is often a vexing problem. Numerous methods have been advocated for its cure, but it must be conceded that no single method of treatment is available which will produce uniformly satisfactory results. The new concept of a hormonal etiologic factor offers a new approach to the therapy of this condition. Should further investigations substantiate the results of my present study, hormonal treatment of endocervicitis may become feasible. Such a study is now in progress. It seems probable that the present unsatisfactory results in the treatment of endocervicitis and erosion are due to the fact that the underlying pathologic cause of this condition has not been recognized. A conservative local treatment of a constitutional hormonal pathologic condition cannot produce good therapeutic effects; on the other hand, the discouraging results of local treatment may induce gynecologists to perform radical operations on the cervix which are unwarranted. It is to be hoped that the further study of hormonal therapeutic measures will eventually develop a cure for endocervicitis and erosions.

I am indebted to Dr. W. H. Stoner of the Schering Corporation for having placed at my disposal the necessary supply of progynon B and proluton.

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DISCUSSION

DR. VINCENT P. MAZZOLA.—These extensive studies demonstrate the changes which occur in the cells of the mucous membrane of the cervix, corresponding to those in the endometrium of the uterus, as shown by endometrial and cervical biopsies. An increase of cervical discharge may be caused by hyperplasia of glands as a

result of increased hormonal stimulus. Hence we should rule out the possibility of increased hormonal influence before making a diagnosis of endocervicitis. He has suggested also that the administration of one of the ovarian hormones can produce a proliferation of certain structures of the cervical mucous membrane, and the other hormone of the ovary, the corpus luteum, can produce a secretive effect and also a condition whereby these so-called erosions, which result from the over-production of columnar epithelium from increased ovarian stimulation, can be transformed into the stratified type.

DR. HARVEY B. MATTHEWS.—A certain proportion of the cervices that are supposed to be infected might come under Dr. Wollner's new etiologic classification. I believe that a certain number of these cervices, even though they are under the stimulation of hormonal secretions, are infected. A certain percentage of them (say 25 or 30 per cent) are or have as their basis an infection, perhaps superimposed on a hormonal stimulating process. But I believe the doctor has started an investigation that may lead us to change our opinions about a certain proportion of so-called cases of chronic endocervicitis with erosions.

DR. SANFORD KAMINESTER.—One question comes to mind. Dr. Wollner finds that with the administration of estrone there is a marked increase in the glandular elements whereas administration of progesterone causes an increase in the squamous cell epithelium.

Several years ago, when the use of estrone was advocated for the treatment of gonorrheal vulvovaginitis in young girls, it was shown by vaginal biopsy that the use of this preparation caused a proliferation of the surface epithelium. Can Dr. Wollner correlate the apparently opposite effect in his material with the previous work?

DR. SAMUEL A. WOLFE.—In a discussion of endocervicitis we must confine our views only to those lesions which are definitely inflammatory in nature. In the acute phase the exudate is composed almost entirely of polymorphonuclear leucocytes. In the subacute phase the lymphocyte or the plasma cell predominates. In a period of fifteen or sixteen years, all cases of erosion of the cervix which I have observed have had an inflammatory basis.

The hyperplasia of the endocervical mucosa produced by estrin is not endocervicitis, but endocervical overgrowth, which is the result of vascular congestion. Leucorrhea is not uncommon in newly wed women or virgins without evidence of infection. Smears are negative and pus cells in the discharge are scant or lacking. The cervix is filled with thick, tenacious mucus and sterility is often an associated symptom. I believe this is the group of cases which Dr. Wollner has described to us tonight. Patients who present an increased growth of glands and secretion of mucus have leucorrhea. Hyperemia from excess coitus, mechanical displacement of the uterus, and unsatisfied sexual contact produces symptoms and findings similar to those experimentally produced by estrin injection.

DR. WOLLNER (closing).—I hope I did not convey the impression that I have found a new cure for endocervicitis. I have simply reported my observations that by the administration of hormones I was able to change the histologic picture in the cervical mucosa, and I expressed the hope that eventually a hormonal cure will be found for this pathology. I do not think that by the administration of progestin alone, we may effect a cure in endocervicitis and erosion cases.

I agree fully with Dr. Matthews in what he said about infected cervices. The question is, whether normal cervices may become infected and subsequently develop the clinical picture of endocervicitis and erosion, or is a hormonal predisposition in the form of erosion the primary factor with which infection becomes associated later on.

According to my observations there is a constant cyclical change going on in the human cervical mucosa, and in certain phases of this cycle histologic pictures are found which resemble inflammatory conditions. At the present time there is a

certain confusion among pathologists as to what should be considered the normal histologic picture in the cervical mucosa.

Observations were reported by several authors which showed a marked proliferation of the vaginal squamous epithelium after the administration of estrin. It must be remembered, however, that my experiments were carried out on patients with nonfunctioning ovaries. It is a question how estrin administration influences normally functioning ovaries. In my reported Case 3, it could be observed that if estrin is given simultaneously with progestin, a marked hyperplasia of the portio-squamous epithelium was present.

HORMONE FACTORS IN THE TOXEMIAS OF PREGNANCY*

With Special Reference to Quantitative Abnormalities of Prolan and Estrogens in the Blood and Urine

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THE responsibility of the placenta for eclampsia and related diseases of pregnancy is an old theory which has been repeatedly revived in various forms. The clinical evidence has always appeared simple and straightforward, for the disease occurs only in pregnancy, and improves rapidly after delivery or the death of the fetus. Furthermore it has seemed unlikely that the fetus itself could be concerned, since cases of toxemia have occasionally been noted with hydatidiform mole. A succession of different substances originating in the placenta have been blamed as medical research has passed through periods of special interest in them. At present it is obvious that the specific hormones elaborated by the placenta—the estrogens, progesterone, and the gonadotropic substances—must be given consideration in this respect.

Although these substances are present in the blood of nonpregnant women, their concentration is greatly increased during pregnancy. It is true that figures for many other constituents of the blood show slight or moderate deviations from nonpregnant levels, but these hormones may increase a hundred or a thousand fold. They are undoubtedly responsible for much that is specific in the physiology of the pregnant woman. Since pre-eclamptic toxemia and eclampsia are diseases occurring only under the peculiar physiologic conditions of pregnancy, it can hardly be questioned that in some sense the hormones play a part in their origin.

*Read at a meeting of The Chicago Gynecological Society, November 18, 1938 and at a meeting of The New York Obstetrical Society, February 14, 1939.

Aided by a grant from The Commonwealth Fund for research in The Physiological Aspects of Obstetrics and Gynecology.

This is giving the question of the relation of the hormones to toxemia an affirmative answer, but one in such a broad sense that it is of little practical value. Nevertheless it is worth while to point out that the present problem is to determine not whether the placental hormones are a factor in the toxemias of pregnancy, but to what extent and in what manner.

THEORETICAL CONSIDERATIONS

To be the cause of pre-eclamptic toxemia, an agent must produce certain clinical symptoms, certain changes in the blood and urine and some characteristic pathologic lesions. Several hypotheses present themselves as to how the many manifestations of the disease may be brought about through the agency of the placental hormones.

a. *Direct Action of the Placental Hormones.*—The first possibility that these substances cause the disease directly is most improbable. The estrogens, progesterone, and prolan are normal substances and their functions are not directly concerned with the body systems apparently at fault in the late toxemias. The production of hypertension, for example, is totally beyond their known scope, nor do the liver and kidney lesions appear to be producible by them. One observation, it is true, exists to the contrary—that of Tschaikowsky,[61] who in 1932 reported degenerative changes in the kidneys, liver, lungs, and blood vessels of mice following the injection of folliculin. Since his time, however, countless mice have been injected with estrogenic and other substances during the course of studies of mammary carcinoma, and no further suggestion has been made of a toxic effect of the estrogens. In excluding the possibility of a direct action of the placental hormones, one must make the reservation that unusual forms of these substances or intermediate products of their metabolism may occur which have a direct effect, but the existence of such toxic substances is at present largely hypothetical.

b. *Intermediate Effect Through Their Influence on General Metabolic Processes.*—A second possibility is based on the observation that the placental hormones in addition to their known effects on genital development and function have secondary actions on more general physiologic processes. Various reports for instance have suggested that the estrogenic substances may raise the basal metabolism, may produce a temporary hyperglycemia by freeing and thus reducing liver glycogen[1] and may even in certain animals cause a rise in the ketone bodies in the blood.[43] More pertinent perhaps have been the recent series of observations showing that the estrogens have the property of causing a retention in the body of sodium and of water (Thorn, Nelson and Thorn[60]). The slight edema of many normal pregnancies and the greater fluid retention of toxemia are conceivably due to this property of the estrogens, made effective by the high concentrations in which they occur in pregnancy.

c. *An Intermediate Effect Through Their Influence on Other Endocrine Glands.*—Perhaps, however, if the three placental hormones are to bring about the triad of hypertension, edema, and albuminuria, they must do so indirectly through their effect on the pituitary, the adrenal, or the thyroid. That these glands may each be affected in function, as well as in structure, by the estrogens is well established. Furthermore, each of these glands has at some time been regarded as a probable factor in toxemia.

1. The posterior pituitary on account of its vasopressor and antidiuretic functions has been particularly studied. The beginning of the pituitary theory dates back at least to a theoretical paper of Hofbauer[31] in 1918. Theory was converted into a burst of animal experimentation by the observation in 1927 of substances from the blood of eclamptics which caused expansion of the melan-

ophores in frogs (Küstner and Biehle[40]) and four years later the reported discovery of pressure raising and antidiuretic substances in the blood of eclamptic patients (Anselmino and Hoffmann[2]). Repetition of Anselmino and Hoffmann's work has largely tended to discredit their results, although some confirmation has been forthcoming (Theobald;[59] Byron and Wilson;[12] Levitt;[41] Hurwitz and Bullock;[36] Page[44]). The studies of Dieckmann and Michel,[15] showing the heightened vascular and antidiuretic responses of patients with toxemia to injections of posterior pituitary extract, give some support to this gland as a factor in toxemia.

2. An anterior pituitary factor in eclampsia has been suggested on the basis of some occasionally described histological changes (Kermauner,[39] Scriba,[49] Shallock,[50] Cushing[14]) and upon the report of a great variety of supposedly anterior pituitary derivatives in the blood of pregnant and pre-eclamptic patients. These include the true gonadotropic hormone of the pituitary; thyrotropic, antithyrotropic (Wiegand[64]) and corticotropic substances (Jores;[37] Fauvet and Münzner[21]); and certain fat and carbohydrate metabolism hormones (Hofmann[32]). Many of these fabulous substances have been reported by only one observer, and little attempt has been made on the part of other workers to confirm or deny their presence.

3. The adrenal has received somewhat less attention than the pituitary. Absence of the usual pregnancy hypertrophy of the adrenal cortex (Fauvet[19]) and low values in corticotropic hormone (Fauvet and Münzner[21]) have led to the suggestion of a cortical deficiency in toxemia. Such a deficiency should, however, give a clinical setting somewhat similar to Addison's disease, very much the reverse of the usual syndrome of eclampsia. One observer (Macchiarulo[42]) has claimed a hyperadrenalinemia in eclampsia.

4. The thyroid has also been held responsible. Several studies have indicated that the usual pregnancy rise in basal metabolism fails to occur or is at least less marked in cases of pre-eclampsia (Hughes[35]). A recent hypothesis (Bartholomew and Kracke[6]; Bartholomew and Colvin[5]; Patterson, Hunt and Nicodemus[45]) has attributed to this relative hypothyroidism a series of events beginning with hypercholesterinemia and progressing through placental endarteritis to placental infarcts and eclampsia.

In now considering particularly the role played by the hormones produced in the placenta, the question at once arises as to why when all pregnant women experience a great increase in the concentration of these substances, do only certain patients react with the symptoms of toxemia? Here, assuming that these hormones do play a significant part in the disease, there are three possibilities.

a. The placental hormones in the toxemic patient may be identical with those of other women and the toxemia occur simply when the constitution is especially susceptible to the normal rise in concentration of these substances in pregnancy.

b. It is possible that these hormones are qualitatively changed in the toxemic patient. This view has been urged by Smith and Smith,[54] who have presented evidence to show that the estriol fraction of the urinary estrogens is decreased, due perhaps to a failure of conversion from estrone. They also offered the hypothesis that the disease might be produced by toxic "breakdown" products of estrogen destruction.

c. Finally, there may be not qualitative, but quantitative, changes in the concentrations of these hormones. Several reports in this country by Smith and other workers and numerous scattered observations in Germany have indicated high levels of prolan and low levels of estrin in pre-eclampsia. The apparent definiteness of the results re-

ported and the evident importance of these substances in the physiology of pregnancy give such a discovery enormous possibilities. The present report is an attempt to check further these observations and is based on the studies of the estrogens, and prolan in the blood and urine of 48 patients in the last trimester of pregnancy.

It is essential that any one who wishes to form an intelligent opinion of work in this field should have some idea of the way in which the reported figures for the estrogens and prolan of the blood and urine are obtained and of the degree of accuracy they represent. He must understand that the biologic methods of assay involve possibilities of considerable error; that the methods of different laboratories have varied too much to permit as yet the acceptance of any absolute values as characteristic even of normal pregnancy, and that finally the range of values for uncomplicated cases is evidently a wide one. Hence for any figure to be regarded as significantly abnormal, it must be compared with values worked out for normal controls by the same laboratory and must differ from these by a considerable margin.

PROLAN DETERMINATIONS

The extraction of the urine was accomplished by the familiar alcohol precipitation procedure of Zondek.[65] By this method 100 c.c. of 95 per cent alcohol were added to 20 c.c. of the twenty-four-hour urine specimen after the latter had been made acid with a few drops of glacial acetic acid. The precipitate was allowed to stand in the refrigerator over night, was centrifuged the following morning, and was then washed several times with ether to remove any contaminating estrogens and allowed to dry. The resulting powder was dissolved in normal saline, adjusted to a pH of 8.5 and brought up to the original volume. The extract was always kept in the ice box until ready for use, the centrifuging being repeated immediately before injection.

For assay of the serum hormones, 50 c.c. of blood was withdrawn and centrifuged at once to separate the cells. In the majority of the tests the serum was assayed directly without further extraction. This seemed wise in order to avoid the inevitable loss entailed by more complicated procedures. Katzman and Doisy[38] for example have shown that percentages of recovery by the various so-called precipitation methods may be as low as 50 to 80 per cent. This use of unextracted serum for prolan determination involves the possible risk of a complicating effect of the estrogens also present in the serum, since it has been shown that estrin may stimulate the test animal's own pituitary to produce luteinizing substance (Fevold and Hisaw[22]). It does not appear, however, that such a possibility can seriously affect the results. The amount of serum estrogen present in toxemias and normal cases is not very dissimilar and its presence should therefore affect all of the cases to a similar extent. Further, it has been shown by Hohlweg[34] that the rat pituitary is not susceptible to estrogen before the twenty-fifth day which, if a correct observation, excludes complicating effects in prolan assay on immature rats.

Prolan assay: Some workers, particularly in Germany, have reported figures in the study of toxemias for both prolan A and prolan B. In view, however, of the persistent uncertainty as to the distinctness of

these two substances and the difficulty of recognizing slight degrees of follicle ripening, the assays in this study were based only on corpus luteum formation.

The test animals used were immature white female rats, approximately 21 days old, and weighing from 20 to 25 gm. The individual doses were divided into five injections given over a period of two days. Ninety-six hours after the first injection the animals were sacrificed and the ovaries grossly examined. By inspection of the ovaries it was possible to determine roughly where the end point would occur. The ovaries of the group of animals just above and just below this probable end point were then serially sectioned and stained. Whenever microscopic examination of these indicated an error in gross reading, the ovaries of the next group of animals, which had been kept in formalin with this possibility in mind, were also sectioned. The final reading depended therefore upon the microscopic search of serial sections for corpora lutea. By this procedure usually not more than 10 and rarely more than 15 ovaries needed to be sectioned for each urine assay.

A few special points need to be emphasized in regard to the procedure of the test.

a. The microscopic sectioning is perhaps of considerable importance. Even after several months of reading ovaries grossly with the naked eye, frequent errors were made. With the dissecting microscope these errors were reduced, but a few mistakes still occurred. If gross readings had been depended upon alone, our average values would have been lower by perhaps a fifth which means that figures for certain individual cases might have been half their actual value.

b. The crude extracts of prolan are somewhat unstable so that the assay should be performed as soon as possible after they have been made. For this reason it is inadvisable to attempt economy by using a few animals only the first week to get a general idea of the strength of the extract and setting up the required animals about the indicated end point on the week following. This has meant in our experience the immediate use of 20 or 25 animals for each assay of urinary prolan.

c. The degree of accuracy which can be obtained when the relatively small number of animals practical for clinical testing are used, remains the most difficult question. For the assay of urine extracts our unit was defined as the amount of prolan which when injected in the manner described will cause the formation of corpora lutea in at least three out of five rats. For the serum which was available in smaller quantities, the unit was taken at the point where two out of three animals were positive. With a group of 405 animals it was found that when half of the extract needed to show one unit was injected, 12.6 per cent of the animals were still positive; when twice this amount was used, 11.2 per cent were still negative. Such variability in response makes results based on one animal totally unreliable and those on five open to some question.

Normal Prolan Levels in Pregnancy.—The excretion of prolan undoubtedly varies greatly at different periods of pregnancy. A very high peak is encountered at about the sixtieth day after the last menstrual period when as much as 300,000 rat units may be present in a liter (Browne and Venning;[9] Evans[18]). After this, there is a gradual

decline in excretion rate, and, by the beginning of the last trimester, the levels are probably at least relatively constant. During this time Browne and Venning[9] report an output of 3,000 rat units, Smith and Smith[53] of 560 rat units in twenty-four hours, and Zondek[65] of 4,000 to 12,000 units per liter.

The average values for 17 normal patients of this study were approximately 4,000 rat units per liter of serum and 2,500 rat units for the twenty-four-hour urine specimens (see Table I).

That a given value is not by any means constant for an individual case is indicated by determinations made during successive weeks before delivery and during labor (Table II). The figures show that a single test is insufficient definitely to determine the characteristic prolan concentrations in a certain patient. There are, however, certain suggestive trends to high or low levels in each of these cases.

TABLE I. NORMAL PROLAN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE RAT UNITS	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					500-999 R. U.	1,000-1,999 R. U.	2,000-3,999 R. U.	4,000-5,999 R. U.	6,000-10,000 R. U.
Serum prolan: Rat units per liter	37.4	17	23	3,871	0	5	5	8	5
Urine prolan: Rat units per 24 hours	37.4	17	23	2,404	5	6	8	4	0

TABLE II. VARIATIONS IN PROLAN VALUES ON SUCCESSIVE DETERMINATIONS AT WEEKLY INTERVALS

PATIENT	WEEKS OF GESTATION	RAT UNITS PER LITER OF SERUM	RAT UNITS PER 24 HOURS
I.S.	34	4,000	2,630
	35	6,667	2,880
	36	4,000	2,040
M.M.	36	1,000	700
	37	1,000	750
	38	2,000	2,000
	39	1,000	1,200
	L.	2,000	2,340
M.G.	37	6,667	4,720
	38	6,667	1,960
	39	4,000	2,420
	40	2,000	1,800
	L.	2,000	2,000
L.D.	37	8,000	2,340
	38	6,667	4,760
	39	6,667	5,200
	40	4,000	8,480
	L.	4,000	6,667

Prolan Values in Toxemias of Pregnancy.—Several reports have been made upon the serum and urinary values for prolan in the toxemias of

pregnancy. The majority of these indicate a rise in prolan but the findings are by no means uniform.

The studies of Smith and Smith must unquestionably be given the most weight. Their first paper[53] reported results on the study of 42 patients in the last trimester of pregnancy and indicated that in 96 per cent of the toxemic and eclamptic patients there was an excess of prolan. Subsequently reported studies[56, 58] by these workers confirmed their early findings by adding more cases and suggested also that a rise in the prolan of the serum occurred six weeks before the appearance of clinical manifestations of toxemia (Smith and Smith[56]), and that this fact might be of practical value in anticipating the approach of symptoms.

Besides this work just cited, scattered reports based on smaller numbers of cases have come from many sources. Ehrhardt[16] reported positive tests for prolan in the cerebrospinal fluid of eclampties and pre-eclampties and negative findings in the fluid of normal women. Apparent confirmation of this finding was later made by Heim[27] and by Hashimoto.[26] Reports on increases of prolan in the urine of eclamptics and pre-eclampties have come from Heim[27] and from Bentivoglio,[7] from Anselmino and Hoffmann,[3] and from Schmidt.[48] Ehrhardt[16] has, however, reported a failure to find high prolan in either the blood or urine of eclamptics. Heim[27] reported several inconsistencies and Schmidt's[48] work, the most extensive of the German studies, indicated that in only 7 of 25 cases of eclampsia and pre-eclampsia was prolan B increased.

The results of the present studies (Table III) do not show consistent differences in the average prolan concentration in the serum or in the rates of urinary excretion between normal and toxemic patients. The figures as first averaged indicated therefore considerable disagreement with the findings of Smith and Smith.

TABLE III. PROLAN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY TOXEMIA

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE RAT UNITS	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					500-999 R.U.	1,000-1,999 R.U.	2,000-3,999 R.U.	4,000-5,999 R.U.	6,000-10,000 R.U.
Serum prolan: rat units per liter	34.6	20	25	3,241	2	4	8	4	7
Urine prolan: rat units per 24 hours	34.0	21	27	2,719	5	4	6	11	1

Search for a reason for this disagreement in results led to a consideration of possible differences in the classification of the toxemias of pregnancy. The Bellevue Hospital classification recognizes three groups of cases among the late toxemias: namely, eclampsia and pre-eclampsia, essential hypertension, and chronic nephritis. The latter group is extremely small in number, so that practically all patients with symptoms of hypertension or albuminuria, not known to have been present in the first trimester of pregnancy, are classed as pre-eclamptic toxemia. It was possible therefore that many of these cases classed by us as pre-eclamptic toxemia might have been regarded as chronic nephritis

TABLE IV. PROLAN IN SEVERE CASES OF PRE-ECLAMPTIC TOXEMIA*

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
Z.R.	32	v	38	++++	175/140	++	1,000	6,560	Medical induction
M.J.	32	0	28	++++	220/130	++++	6,667	1,240	Hysterotomy
H.S.	19	0	23	++++	170/110	++	----	5,200	Hysterotomy
L.S.	33	0	26	++++	176/110	++	6,667	4,160	Hysterotomy
D.M.	26	ii	24	++++	198/110	++++	2,000	3,000	Hysterotomy
			25	++++	186/110	++++	2,000	2,720	
			26	++++	190/114			4,133	
Average							4,083	4,089	

*The averages are based on the mean of the several determinations for a given patient.

TABLE V. PROLAN IN TOXEMIA WITH DEATH OF FETUS*

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
V.H.	18	0	32	++++	158/98	+++	4,000	4,040	Macerated stillbirth 12 days after first test
			33	++++	210/160	+++	----	835	
A.M.	27	0	33	0	170/110	++	2,000	985	Macerated stillbirth 31 days after first test
			37	++	150/115	++	1,000	1,250	
			38	+	140/110	+	2,000	1,310	
L.J.	27	iii	40	++	180/108	++	2,000	4,160	Macerated stillbirth 3 days after test. Fetal heart heard day of test
A.R.	29	i	39	+	168/110	+	1,000	1,205	Macerated stillbirth 10 days after first test
			40	0			1,500	810	
L.I.	26	i	32	+	118/84	++	4,000	457	Macerated stillbirth 7 weeks after first test
			36	+	174/125	+++	2,000	845	
Average							2,600	2,169	

*Only first figure is used in final averages of toxemic cases.

by other workers. We therefore selected out four special groups, each unfortunately represented by only a few cases.

1. *Severe Cases of Pre-eclamptic Toxemia.*—The first group consisted of five cases and are those severe enough to have warranted termination of the pregnancy (Table IV). The cases of this severe group had with one exception some elevation of the prolan in either the serum or the urine.

2. *Cases of Late Toxemia Culminating in Fetal Death.*—The next group included the cases in which death of the fetus occurred within a few weeks after the tests were undertaken. The fact of impending fetal death suggests a serious degree of toxemia, but it might not unreasonably be expected that associated placental

TABLE VI. PROLAN IN ECLAMPSIA

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
E.H.	39	i	28	0	210/140	+++	1,000	680	Convulsion 2 days before test. Delivery 1 day after
S.McL.	37	i	32	++++	172/96	+++	----	2,630	Patient was delivered and died next day
ALo.M.	24	0	40	+++	142/92	+	4,000	840	Post-partum convulsion and specimen

TABLE VII. PROLAN IN AVERAGE CASES OF TOXEMIA

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
F.C.	34	iv	40	0	152/100	+	1,000	815	Very mild case
A.C.	30	iii	36	+	162/92	+++	1,000	692	Toxemia with previous baby
G.P.	20	0	40	++	158/92	++	4,000	2,570	Headaches. B.P. in labor 170/108
A.C.	30	ii	40	++	158/90	0	2,000	4,040	B.P. 170/96 in labor
L.D.	20	0	37	2.9g	145/110	++	8,000	2,340	Severe case. Induction considered
			38	3.8	170/114	++++	6,667	4,760	
			39	5.4	158/124	+++	6,667	5,200	
			40	4.2	188/118	+++	4,000	8,480	
Average							2,866	2,662	

damage would result in diminished hormone production. The prolan levels of both blood and urine were found to be lower than in the severe cases (Table V) of the last group, and the serum values were even somewhat lower than those for the normal women.

3. *Eclampsia.*—There were three cases (Table VI) which developed eclampsia. Neither of the two with convulsions ante partum showed signs of an increased prolan, although repeated specimens could not be examined. In the third case, which has not been used to compile the average values, the convulsions developed after labor. The low urinary prolan in this case is not surprising considering the rapidity with which these hormones disappear after delivery. The serum prolan in this case was perhaps a little high.

4. *Mild Pre-eclamptic Toxemia.*—The remaining cases have been classed as mild, because they were unassociated with any special complications (Table VII). In all but one case of this group the prolan was not different from the normal. One patient from whom four specimens were obtained showed consistently high levels. She was unquestionably the severest of the five and might more properly belong to the class in which termination of pregnancy was carried out.

Conclusions in regard to the prolan in the toxemic cases of this series were simply these. The general average and range for the prolan concentration of the serum and the twenty-four-hour excretion were not significantly different from those of the normal controls. Selection of the severer cases with all of the manifestations of pre-eclamptic toxemia resulted, however, in the isolation of a group in which the prolan of the urine or serum was a little high.

ESTROGEN DETERMINATIONS

Preparation of Specimen.—The amount of estrin in the urine of pregnant patients is large enough so that concentration before assay is unnecessary. The estrogens occur in the urine principally in a combined form which is not determinable by bio-assay. In order to free the combined estrogens, all urines were "hydrolyzed" by boiling for two hours after the addition of 10 per cent by volume of concentrated hydrochloric acid. The figures for the urine represent then the so-called "total estrogens." The sera were not so treated and only free estrogen was therefore determined here.

Estrogen Assay.—The assay was conducted according to the typical Allen-Doisy test on spayed female rats, weighing from 125 to 175 gm. Each rat received a "priming" dose of an estrogen ten days before the assay, and animals unresponsive to such treatment were not used. Injections for the test were given in a total of four doses on two successive days and vaginal smears made four times on the third and fourth days.

The unit adopted by us was complete cornification with complete absence of both nucleated epithelial cells and lymphocytes in three-fourths of the animals. At first four, and later eight, animals were used at each dose level. The studies of various workers have shown that the rat unit may vary from about 5 to 40 international units (Hain and Robson,[25] Hinglais and Hinglais,[30] Bülbring and Burn[11]. Repeated assay of crystalline estrone has shown that the rat unit, as defined by us for this work, has amounted to about 35 international units. This will explain why our figures for estrogens in pregnant urine are considerably lower than those reported by many other investigators.

The definition of the unit, as described, was originally adopted with a view toward increased accuracy, since it was felt that complete cornification was easier

to recognize than any special proportion of cells. There appears to be no great disadvantage in using such a large unit in the assay of the urine in pregnancy, but special difficulties occur with the serum. Here one rat unit is rarely contained in less than 5.0 c.c., and since the supply of material for testing is limited, accurate quantitative studies are not feasible. Some basis for comparison was obtained by estimating the degree of estrus reaction in each smear, and grading each with figures from 0 to 4, according to the method originally described by Frank[23] for tests on the blood of nonpregnant women. Four animals were each injected with 3.0 c.c. of serum, the height of the reaction in each noted and the average expressed by a single figure.

The accuracy of the figures for the estrogens based on rat assay is apparently less than for the prolan. This statement is based on studying the reaction of a group of 474 animals which showed that, when one rat unit is fixed as the amount which will cause complete cornification in at least 75 per cent of the animals, then with half of this dose a quarter of the animals are still positive and with double the dose, 15 per cent are still negative.

Normal Estrogen Values in Pregnancy.—The changing methods of hydrolysis, extraction and assay of estrogenic substances in the urine have resulted in continued alteration in what have been regarded as the normal values. In 1928 Aschheim and Zondek[4] reported 6,000 to 10,000 mouse units per liter in the last trimester of pregnancy. Smith and Smith's figures in 1934 before hydrolysis was used were 5,800 rat units for twenty-four hours. Since then the figures have mounted rapidly. Cohen, Marrian and Watson[13] reported by colorimetric methods a daily excretion of 22 mg. of combined estriol and 3 mg. of estrone which has an equivalent value of about 250,000 mouse units. Smith and Smith[58] give perhaps slightly higher values. Goldberger[24] found lower values for "total estrins" with a peak of 180,000 mouse units at the thirty-third week followed by a fall to from 40,000 to 45,000 mouse units during the last month. Goldberger's[24] figures indicate the marked variations which may be present in the excretion curves of even a single case, and Browne and Venning[9] suggest the occurrence of cyclical fluctuations. With the serum, the reported figures have been still less consistent, owing of course to the small amount of material available for tests. Smith and Smith[53] obtained

TABLE VIII. ESTROGEN EXCRETION AND SERUM CONCENTRATION IN LAST TRIMESTER OF NORMAL PREGNANCY

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					0-499 R.U.	500-999 R.U.	1,000-1,999 R.U.	2,000-2,999 R.U.	3,000-3,999 R.U.
Urine Rat units a day	37.4	17	23	1,311	2	8	6	5	2
Serum					SERUM. REACTION TO 3.0 C.C.				
Reaction to 3.0 c.c.	37.4	17	23	1.58	0-0.5	0.5-0.9	1.0-1.9	2.0-2.9	3-4
					4	2	5	8	4

positive reactions with 3 c.c. or less in their early reported normals. Bickenbach and Fromme[8] never obtained a positive with less than 10.0 c.c.

The twenty-four-hour excretion of "total estrin" in twenty-three assays of this study averaged 1,300 rat units (Table VIII). With the large rat unit used, this corresponds to about 45,000 international units, approximately the figure reported by Goldberger[24] for his case during the last few weeks of pregnancy. As regards serum, a full rat unit was practically never demonstrable by the injection of 3.0 c.c. of serum.

Figures obtained by repeated assay of several specimens on successive weeks again showed that wide fluctuations may occur in the rates of excretion (Table IX). The figure obtained by one determination does not therefore characterize the behavior of the estrogens for a given case.

TABLE IX. VARIATIONS IN ESTROGEN VALUES ON SUCCESSIVE DETERMINATIONS AT WEEKLY INTERVALS

PATIENT	WEEKS OF GESTATION	URINE	SERUM
		RAT UNITS PER DAY	REACTION TO 3.0 C.C.
I.S.	34	1,646	2.5
	35	1,800	1.75
	36	3,406	1.00
M.M.	36	585	2.00
	37	2,380	2.25
	38	1,300	3.25
	39	530	2.25
	L	800	2.25
M.G.	37	295	0.75
	38	245	2.50
	39	300	2.75
	40	450	1.25
	L	500	1.25
L.D.	37	585	2.20
	38	2,380	2.25
	39	1,300	3.25
	40	530	2.25
	L	166	1.25

Total Estrogens in Toxemias of Pregnancy.—Relatively low values for estrogenic hormone in the urine and blood of toxemic patients were reported by Smith and Smith[53, 56, 58] in 1934, 1935 and 1937. This coupled with the simultaneously high prolan has laid the basis for an hypothesis of an "imbalance" between the two hormones as a factor in toxemia. By means of a chemical test, Savage and Wylie[47] have corroborated the findings of low estrins in toxemic cases. They found, however, that values were low in the so-called chronic nephritics as well as in the cases of pre-eclamptic toxemia.

The summary of the results of 62 determinations in toxemic patients shown in Table X indicates what are probably significantly lower estrogen values than in the normal cases. The average figure of 584 rat units for twenty-four-hour excretion is less than half of

the normal figure. The usual reaction to 3.0 c.c. of serum was also definitely weaker in the toxic cases. Although exceptions occurred, the excretion in the toxemic cases was as a rule under 1,000 rat units, that for the normal cases usually above that figure.

TABLE X. ESTROGEN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY TOXEMIA

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					0-499 R.U.	500-999 R.U.	1,000-1,999 R.U.	2,000-2,999 R.U.	3,000-3,999 R.U.
Urine Rat units a day	34	21	31	584	11	14	5	1	0
Serum					SERUM REACTION TO 3.0 C.C.				
Reaction to 3.0 c.c.	34	21	30	0.92	0-0.5	0.5-0.9	1.0-1.9	2.0-2.9	3-4
					10	9	6	4	1

Separation of these cases into the four special groups previously used in reporting prolan studies showed little difference in the figures for the different classes of cases (Tables XI, XII, XIII, and XIV). There was nothing to distinguish the severe cases from the mild ones. The approaching death of the fetus was not heralded by any rise or fall in the estrogen figures. The values for urinary estrogens of the two eclamptics studied ante partum were, however, the lowest of any group. The consistent and rather wide divergence from the normal of the estrogen values in the toxemias makes it appear then that here an actual difference exists.

TABLE XI. TOTAL ESTROGENS IN SEVERE CASES OF PRE-ECLAMPSIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
Z.R.	32	v	38	++++	175/140	++	536	0.75	Medical induction
M.J.	32	0	28	++++	220/130	++++	1,033	0.66	Hysterotomy
H.S.	19	0	23	++++	170/110	++	325	—	Hysterotomy
L.S.	33	0	26	++++	176/110	++	336	0.00	Hysterotomy
D.M.	26	ii	24	++++	198/110	++++	225	0.25	Hysterotomy
			25	++++	186/110	++++	1,400	—	
			26	++++	190/114	++++	775		
Average							600	.45	

TABLE XII. TOTAL ESTROGENS IN TOXEMIA WITH DEATH OF FETUS

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
V.H.	18	0	32	++++	158/98	+++	835	0.50	Macerated stillbirth 12 days after first test
			33	++++	210/160	+++	840	0.50	
A.deM.	27	0	33	0	170/110	++	820	0.25	Macerated stillbirth 31 days after first test
			37	++	150/115	++	1,562	0.00	
			38	+	140/110	+	655	1.25	
L.J.	27	iii	40	++	180/108	++	1,300	0.75	Macerated stillbirth 3 days after test
A.R.	29	i	39	+	168/110	+	301	0.75	Macerated stillbirth 10 days after test
			40	0			400	0.75	
L.I.	26	i	32	+	118/84	++	846	1.00	Macerated stillbirth 7 weeks after first test
			36	+	174/125	+++	422	0.50	
Average							820	0.64	

TABLE XIII. TOTAL ESTROGENS IN ECLAMPSIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
E.H.	39	i	28	0	210/140	+++	377	----	Convulsion 2 days before, delivery 1 day after
S.Mc.L.	37	i	32	++++	172/96	+++	395	1.75	Delivery and death 1 day later
A.LoM.	24	0	40	+++	142/92	+	97	0.25	Post-partum specimen

EXCRETION OF PREGNANDIOL

In the past both an excess and a lack of corpus luteum have been blamed for toxemia. Treatment by corpus luteum is now being advised (Robson and Patterson[46]), and abnormal values for corpus luteum in the placentas of toxemic patients have been reported (Smith and Kennard[52]).

The isolation by Venning and Browne[62] of pregnandiol from human pregnancy urine and the recognition that this substance was an inactive excretion product of progesterone have led to the possibility

TABLE XIV. TOTAL ESTROGENS IN AVERAGE CASES OF TOXEMIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
F.C.	34	iv	40	0	152/100	+	679	0.5	Very mild case
A.C.	30	iii	36	+	162/92	+++	346	1.00	Toxemia with previous baby
G.P.	20	0	40	+	152/92	++	643	0.25	Headaches. B.P. in labor 170/108
A.C.	30	ii	40	++	158/90	0	673	2.00	B.P. in labor 170/96
L.D.	20	0	37	2.9	145/110	++	585	2.20	Severe case. Induction considered
			38	3.8	170/114	++++	2,380	2.25	
			39	5.4	158/124	+++	1,300	3.25	
			40	4.2	188/118	+++	530	2.25	
Average							708	1.30	

that its measurement might give a practical method of studying corpus luteum function. Reports have already been made that the excretion of pregnandiol is diminished in the toxemias of pregnancy (Weil;[63] Smith and Smith[54]).

The preliminary figures of Table XV confirm these observations. It will be noted, however, that again there are exceptions and that a few toxemic patients excrete more pregnandiol than do certain normals. One case of special interest showed unusually low values preceding the death of the fetus.

TABLE XV. EXCRETION OF PREGNANDIOL

	NUMBER OF TESTS	AVERAGE DAILY EXCRETION IN MILLIGRAMS	RANGE
Normal cases	14	47.8	13.0-128.0
Toxemic cases	18	17.4	0 - 51.2

Cases of Premature Separation of the Placenta.—It has been maintained by Shute[51] that certain types of late pregnancy toxemia, associated with retroplacental hematomas, showed a high estrin in the blood serum of the patients. He reports that of 66 such cases studied by him, 82 per cent showed an excess of blood estrogens and that 85 per cent of 39 cases of severe abruptio placentae also showed such an excess. Heim has reported high values for urinary prolan in cases of premature separation of the placenta.

In Table XVI are given the values for prolan and estrogen in 8 cases of bleeding of unexplained origin, probably due to minor de-

TABLE XVI. PROLAN AND ESTROGENS IN CASES OF UTERINE BLEEDING

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA		PROLAN		ESTROGENS		COMMENT
				ALB.	B.P.	SERUM	URINE	URINE	SERUM	
M.S.	24	i	36 37	0 0	108/70 115/70	4,000 6,667	3,136 1,813	1,306 906	1.0 0.75	Slight bleeding at 32 weeks and at onset of labor
P.N.	18	i	38	0	116/78	4,000	8,744	729	1.75	Bled intermittently 6 weeks before labor
I.D.	29	0	28	0	118/68	1,000	1,810	452	1.00	Bled constantly 6 weeks before labor
M.N.	22	0	20	0	110/68	1,666	1,136	4,284	0.25	Bled 4 weeks at 18 weeks
M.N.	24	iv	26	0	110/76	2,000	1,810	754	0.50	Bled at 24 weeks
S.F.	22	0	30	0	106/70	2,000	1,335	293	0.25	Bled constantly 1 month before test
F.R.	19	0	40	0	110/60	4,000	2,555	1,916	3.75	Bled 7 days before labor
M.B.	21	ii	32	0	120/68	1,000	4,680	780	1.50	Bled constantly from 35th week
Average of mild cases						2,625	3,068	789	1.26	
M.D.	43	xi	32	+	160/106	4,000	4,257	212	0.25	Premature separation. Stillbirth
R.F.	21	0	35	++++	130/98	4,235	----	----	1.00	Complete separation. Stillbirth

grees of placental separation, and in 2 cases of typical complete separation of the placenta. There is no evidence of excessive estrogen in any of these patients. It is not certain, however, that this group is clinically identical with that described by Shute as being characteristically associated with an excess of estrogen.

DISCUSSION

The significance of these hormone differences between normal and toxemic patients is still a matter for theory. According to one view a disturbed balance between hormones may actually be the cause of toxemia. A simpler view is that the abnormalities are merely the result of the disordered physiology of the toxemic patient.

The excretion of the estrogens for example is dependent upon a great variety of conditions. There is first the rate of production which occurs in the placenta. There is second the degree of destruction or conversion into an inactive form which may occur in the liver or kidney. There is finally the factor of kidney excretion, although there is less belief than formerly in a renal threshold. With the amount of estrogen in the urine dependent on placental, renal, and hepatic function, it is not surprising that the values in blood and urine may be altered in such a disease as pre-eclamptic toxemia. Somewhat similar conditions undoubtedly govern urinary pregnandiol values, and probably blood and urinary prolan concentration.

CONCLUSIONS

1. In a broad sense there can be little doubt that the placental hormones are a factor in the late toxemias of pregnancy.

2. The tests for these hormones give only approximate values.

3. The blood and urinary figures for these substances show large normal variations when different individuals are compared and even when different specimens of the same individual are contrasted.

4. In a series of 21 cases of late toxemia and 17 cases of normal pregnancy, there was evidence of a frequent but not invariable lowering of the estrogen values in the toxemic cases and of an elevation of the prolan values in a few cases only. A lowered pregnandiol excretion was also noted in a shorter series of determinations.

5. No hormone abnormalities were noted in 8 cases of unexplained bleeding and two cases of premature separation of the placenta.

6. The hormone changes observed in the toxemic patients are perhaps associated with the cause of toxemia, but may simply be the result of the disturbance of kidney, liver, or placental physiology.

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DISCUSSION

DR. CARL R. MOORE.—I am certainly glad to be one of you to congratulate Dr. Taylor on his conservatism—conservatism not only in handling the theoretical aspects of such a problem as he presented but likewise in handling the data which he has collected in an endeavor to throw light upon a particularly difficult problem. Conservatism and hard work are the two greatest needs, it seems to me, in such a field as this. Conservatism, if for no other reason than the fact that in this more or less newly developed field of hormones, some have had hopes that many baffling problems, unsettled before, would be settled by the new technique. For this reason we must obviously consider these problems with a great deal of open-mindedness and not make an attempted analysis with preconceived ideas. As you know, hormones have been looked to to cure practically everything from temperamental disturbances to wrinkles on the face and defects in hearing. Hormones do alter the physiology of the organism and abnormal physiology does alter hormone secretion.

In an attempt to analyze Dr. Taylor's paper there are just two main aspects I wish to mention. It seems to me that he has very adequately considered the theoretical aspects, or the possible bearing of the hormones in relation to the conditions he is describing. Obviously you would not expect one such as myself, who works with

rats, guinea pigs, and other low forms, to be very well versed on the treatment of eclampsia, because we do not encounter such disturbances in our experimental material. We are very thankful that we can carry out hormone studies in animals that are normal or modified by our choice. We do not work with sick animals; we discard them. Dr. Taylor has apparently considered very carefully the possible angles on the physiological side, that is, the bearing of the hormones on this disease. I am certainly not in position to suggest any which he has omitted.

The second point that I wish to emphasize clearly in your minds is that Dr. Taylor has not tried to prove that hormones cause eclampsia or that any one hormone causes eclampsia, he has merely attempted to determine whether there is a deviation in hormonal output detectable in individuals showing this condition when compared with those whose pregnancy is normal. If he had been able to demonstrate that there were gross differences he still would not be in position to maintain that the different hormonal condition was the cause of the underlying condition. He has very emphatically pointed out that excessive hormone output might be merely an accompanying condition and not the cause.

I have found Dr. Taylor's talk so satisfying that I do not seem able to criticize the many approaches he has considered as bearing on the theoretical aspects. There is one point that should be considered if real progress is to be made in this field. Only those of you who have attempted to make this type of analysis realize the multitude of difficulties in arriving at trustworthy results. Dr. Taylor has pointed out that it is impossible for any one individual to take any other individual's findings because standards of procedure and end points differ so widely. It would seem that not only in this but in many other diseases of this kind cooperative work would be well worth while, in which a central agency would handle all the analyses. Working even with normal animals on two sides of the Atlantic Ocean very different results are reported, not because the animals are so different but because different methods of procedure, such as treatments, extractions and assays, are so at variance. Cooperative projects would seem very much worth while.

I am not certain whether Dr. Taylor has not been too conservative. I have commended him for it, but often averages are sometimes very misleading. After all we must depend on averages until we have clear-cut results. A small number of cases in which variations of from 800 to 1,000 per cent are included may completely eliminate any suggestions indicated in the collection of data when only averages are considered. It is obvious that more cases are needed. One could well use a graph of findings from 100 normal women, not in the thirty-fourth week but in all weeks of pregnancy and perhaps have a reliable standard of reference with which to compare hormonal assays from pathologic cases. Such cooperative projects could be established in large cities. A great deal can be said for a cooperative project carried out by one set of investigators as a foundation for establishing basic principles which are needed to answer the question, not whether these hormones are the cause of this condition, but merely whether they vary from the norm found during normal pregnancy. Dr. Taylor has carried out a great deal of work but he has been compelled to report to you only negative results. He has been unable to settle one point firmly in his own mind with this work, Is there a difference between the normal condition and the pathologic one from the standpoint of the output of these individual hormones? It is perfectly obvious that a discussion of results of different investigators which are not comparable is futile and utterly useless. It is also perfectly obvious, I think, that great advances would be made if we could reproduce in some suitable animal the experimental condition now under consideration, but so far as I know there is little hope of its accomplishment.

DR. WILLIAM J. DIECKMANN.—Innumerable attempts have been made during the past few decades to link eclampsia with an abnormal function of one or more of the glands of internal secretion. The rapidity with which an eclamptic patient may recover is well known, and the pathologic changes, if present, are usually too meager to account for the many signs and symptoms of the disease and the marked physical and chemical alteration in the blood, urine, and tissues. The most logical theory is that eclampsia is caused by a disturbance in the normal physiology of an

organ or a gland. Such a condition could respond to treatment very quickly. Thus, the idea of a hormonal imbalance is intriguing.

It seems to be the consensus of opinion, although the amount of accumulative data is relatively small, that eclampsia and pre-eclampsia are characterized by a low estrogen and high prolan concentration in both blood and urine. Smith and Smith in their last report state that "the manifestations of pre-eclampsia coincide with changes in the urinary values for pregnandiol, estrone, estriol, and estradiol which reflect a progestin deficient metabolism of the estrogens." They suggest "that the vascular phenomena which are responsible for endometrial flow and pre-eclampsia may be brought about by a toxic concentration of nonestrogenic breakdown products resulting from destruction of the estrogens." They have treated several presumably pre-eclamptic patients one of whom received 170 mg. of progesterone and 2,550,000 I.U. of estradiol benzoate over a period of nine days without any clinical change. Incidentally the cost of these substances would amount to $382.00. Dr. Taylor has been very conservative in his conclusions, stating that the test for hormones gives only approximate values and that the changes may perhaps be associated with the cause of toxemia or they may be the result of the disturbances of kidney, liver, or placental physiology.

The work of Thorn and Harrop and of Kenyon and co-workers lends some support to the theory that a disturbance of the hormone balance may be associated with pre-eclampsia. These investigators noted that a retention of sodium together with associated water may be produced in both dog and man by the administration of estrone, estradiol, progesterone, pregnandiol, and testosterone. The retention was sufficient to produce an increase in body weight. Similarly, the increase in weight often seen before menstruation may possibly be due to the alteration in concentration of these hormones.

Stander has reported marked changes in the uric acid, lactic acid, and CO_2 content of the blood in toxemic patients. We have emphasized the marked alterations in blood and plasma volume and changes in concentration of serum protein, hemoglobin, etc., and correlated these changes with the clinical condition of the patient. Some investigators have attributed eclampsia and pre-eclampsia to these physicochemical changes. In view of these extensive alterations it is not improbable that the hormones are also affected, and the changes in concentration and excretion may be, as also suggested by Taylor, a result instead of a cause of pre-eclampsia.

The obstetrician has not decided what eclampsia, pre-eclampsia, or toxemia of pregnancy are either clinically or pathologically, and yet he has been observing these conditions for many years. I have been especially interested in the study of the toxemias of pregnancy for the past fifteen years, and yet my diagnoses as to type have frequently been incorrect especially if made during the hospital period. None of the published reports of hormone studies have followed patients long enough after delivery to confirm their diagnosis of the kind of toxemia. Furthermore, I believe the same patient should be followed through a subsequent pregnancy to determine if the hormone assays are again abnormal or normal.

Eclampsia according to Küstner can be cured with thyroxin. Hoffmann and Anselmino have stated that the thyroid hormone content is tremendously increased in the blood of eclamptic patients. We have found daily doses of 1 or 2 gr. of thyroid to be of no value in pre-eclampsia, perhaps because this condition does not permit protracted medical treatment. However, in the patient with vascular-renal disease with marked albuminuria, thyroid therapy seems to be of some value in reducing, or at least preventing further increase in the amount of protein excreted per 24 hours; other therapeutic measures are also used. Nicholson has stated that the more normal the thyroid the less likely that toxemia will develop. Approximately 7 per cent of our toxemic patients had hyperthyroidism; the diagnosis of toxemia was based primarily upon the hypertension which was usually present in these patients.

The adrenal cortex enlarges in pregnant animals, and it has been stated that the hypertension of toxemia is due to an increased amount of adrenalin. Adrenal cortical extract because of its effect in increasing blood and plasma volume and also its effect on the renal threshold for sodium has been suggested in the treatment of eclampsia, but, so far as I know, has not been used.

Cushing described an invasion of basophilic cells from the anterior lobe and pars intermedia of the pituitary into the posterior lobe. He postulated that vasopressin came from the anterior lobe because the posterior lobe does not look like secreting tissue. All reports to date do not confirm Cushing's theory. The anterior lobe of the pituitary does enlarge during pregnancy, but no one has noted any unusual change in association with toxemia of pregnancy. Cushing's comment that the posterior lobe does not look like secreting tissue is interesting because certainly the placenta does not look like an organ of internal secretion, and yet it is supposed to produce enormous quantities of female hormones.

Anselmino and Hoffmann stated that there was an increased amount of the pressor and antidiuretic components of the posterior lobe secretion in the blood of eclamptic and severe pre-eclamptic patients. However, five groups of investigators have been unable to confirm this work. Michel and I stated that the blood pressure of the true eclamptic and pre-eclamptic patient gave a marked rise if the patient was injected with two minims of pituitrin. All other nonpregnant and pregnant patients, even if the latter had essential hypertension or vascular-renal disease, gave little or no response. This test has been used by us to aid in the differential diagnosis of pre-eclampsia from other toxemic conditions. Our work has been used to support theories as to the cause of eclampsia which ascribed the disease to posterior lobe hormones, but the mere fact that pre-eclamptic patients show an unusual response to the injection of pituitrin does not warrant the statement that eclampsia is due to an abnormal amount of posterior lobe secretion.

According to the chemists' conception the hormone studies to date are not quantitative but are roughly qualitative. However, they offer possibilities as to the diagnosis of pre-eclampsia when it is present and also a possible means of detecting patients who may develop pre-eclampsia. It is unwarranted to draw conclusions from a study of 50 or 100 cases when the methods of analysis are crude and the variation in both normal and abnormal overlap. Furthermore, to treat toxemic patients with hormones and other drugs and ascribe improvement only to the hormone is incorrect. The clinical condition of toxemic patients is so variable that a large number must be treated with *only* the hormone in question before any conclusions are justified.

DR. FRED L. ADAIR.—I would like to compliment Dr. Taylor on the excellence of his material and its presentation. I would like to mention the parathyroids in connection with a consideration of hormones in their relations to the toxemias and metabolism of pregnancy. There is a case in the literature in which thyroidectomy was done and the parathyroids injured. The patient was operated upon after three normal pregnancies. During the subsequent pregnancy she developed tetany which was controlled by the use of parathormone. Dr. Laura DaSef and Dr. Bengt Hamilton made a study of parathyroids in pregnancy in our clinic, indicating that there are certain definite parathyroid changes during pregnancy shown by an increase of parathormone during pregnancy. We have made no such thorough study as Dr. Taylor has made of the hormones. However, we have done some work, and with the permission of the Chairman, I would like to ask the courtesy of having Dr. Ruth Watts discuss it.

DR. RUTH WATTS, PH.D.—I wish to join Dr. Moore in commending Dr. Taylor for his scientific approach to a problem in a field in which the literature is so filled with data of little significance.

I wish to add a point or two in review of Smith's work. If you inspect his work you will find that the individual variation in both groups is very great. The standard deviation in such groups can become as large as the value itself. It then becomes impossible to evaluate a single determination by comparison with a mean value unless that value is an extreme one. I have some slides to show, some results of a study Dr. Adair and I have undertaken. I am showing the first one for two reasons, first, to confirm Dr. Taylor's survey on relation of dose to response, and the second, to present our method of assay because I want you to judge the reliability of our data.

We have assayed each of the gonadotropic and estrogenic hormones by the characteristic curve method; two consecutive twenty-four-hour urine specimens were assayed for each individual; twenty 21-day-old rats were used in the prolan assay and 40 castrated rats for the assay of estrogenic hormone. After injecting the entire group of animals at one dose level, the assay value was obtained by reading from the chart the value corresponding to the percentage response.

The second chart is a graphic presentation of the actual values (R.U. per twenty-four hours) obtained in our study. There is a marked tendency toward the increased excretion of gonadotropic substance and a decreased excretion of estrogenic substance in the toxemic group. Although the mean values show a definite difference between the normal and the toxemic groups the extreme variation in the individual values composing these groups makes it impossible to compare safely an individual determination with this mean value. In the normal group there seems to be a relation between the amount of gonadotropic and estrogenic hormone excreted by each individual, i.e., an individual excreting a relatively large amount of one will also excrete a relatively large amount of the other. This is illustrated in the chart by the slope of the line connecting those two values for each individual. The chart is constructed so that in the normal group the scale of the range of the twenty-four-hour values of estrogenic substance is equal to the scale of the range of the twenty-four-hour values of prolan. In the toxemic group the general slope of these lines is altered and assumes an opposite direction.

In the next chart, this relationship is expressed as a ratio of the excretion of prolan to estrogenic substance. The hormone analyses expressed in terms of this ratio seem to show less variability due to individual variation than was shown in the previous chart. These ratios are fairly constant in the normal group and are definitely increased in the toxemic group.

In conclusion, our work shows great variation in actual values of gonadotropic and estrogenic substances, a fairly constant ratio between these two substances during normal pregnancy and an increase in the ratio during pregnancy in the toxemic group.

DR. ALEXANDER GABRIELIANZ.—In Dr. Taylor's paper there is a statement about pituitary and pituitary-like substances as if they were the same substances. In my opinion there is a great biologic difference between the two. If an immature hypophysectomized mouse is injected with pituitary-like substance, without reference to dosage, a follicle never appears on the ovary, but if pituitary substance is injected into an immature hypophysectomized mouse, then a follicle appears on that ovary. I wish to ask Dr. Taylor if he noticed any other difference between these two, pituitary substance and pituitary-like substance.

DR. HOWARD C. TAYLOR, JR. (closing).—Dr. Moore's suggestion that hormone studies of this type should be developed as a cooperative project seems to me most important. The technical work of assay ought perhaps to be done in a department of zoology, rather than in one of medicine. It is clearly work for which the biologist is better equipped than the physician. Such investigations could be well handled by two such departments, the physician diagnosing and following the case clinically, the biologist helping to outline the experiment and supervising or performing the work of assay. With the clinician such biologic studies are a heavy burden, and a somewhat unfamiliar one, to be carried in addition to the regular work of the ward and practice.

I am very much interested in Dr. Watts' determinations. My understanding is that she found a high prolan and a low estrin in most cases, but that she also noticed several exceptions. This is of course in confirmation of much previously reported work, and especially significant since the prolan was determined by a different end object from the one usually employed. The concept of an "imbalance" is, however, in my opinion a very misleading one. It implies some sort of a reciprocal physiologic relationship between these two substances, and there is little reason yet to think that such a definite relationship exists. Absolute values are significant but I do not think that a quantitative relationship of one to the other is yet established.

I did not say that pituitary-like substance of pregnancy urine and true gonadotropic substance were identical. I was speaking of prolan A and B, which are both reactions occurring after the injection of pregnancy urine. I showed on my slide four different ovaries, one which showed no follicle, and came from an untreated infantile rat; one which showed many small follicles following injection of menopause urine; one with a single large follicle from the injection of pregnancy urine, and one with a corpus luteum, also following the injection of pregnancy urine. Whether one will get a large follicle or a corpus luteum following the injection of pregnancy urine depends, in part at least, on the amount of substance injected. There will be a very large difference in the number of units of pregnancy urine gonadotropic substance reported depending on whether one takes as an end point follicle ripening (prolan A) or corpus luteum formation (prolan B). The latter is a much more reliable end point, because partly ripened follicles may begin to occur normally in quite young rats and mice.

VESICOVAGINAL FISTULA AFTER COMPLETE ABDOMINAL HYSTERECTOMY

Description of Technique Used for the Cure of Two Cases by the Vaginal Route

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(From the Clinic of the Woman's Hospital)

IN RECENT years numerous articles have appeared describing improvements in the operative technique of complete abdominal hysterectomy. The advantages of this procedure over subtotal or supravaginal hysterectomy have been emphasized and some gynecologists have been so impressed with its benefits that they have adopted complete hysterectomy as a routine procedure in cases demanding removal of the corpus uteri.

Experience with large series of complete hysterectomies will ultimately determine whether this more extensive operation, as a more or less routine procedure, is justifiable. When examination of the cervix reveals extensive birth injuries or marked chronic infection associated with conditions demanding removal of the corpus uteri, there can usually be no argument against complete hysterectomy. However, experience has shown that the milder cervical infections and erosions can be readily cured by electrocoagulation at the same time that supravaginal hysterectomy is done. By combining these two procedures complete removal of the uterus is frequently unnecessary.

It can hardly be denied that complete removal of the uterus is, on the whole, technically much more difficult than the supravaginal procedure and that the operation is attended by a somewhat higher incidence of accidents and unavoidable complications.

Among the most distressing of these is that which results in urinary incontinence from injuries to the bladder. Vesicovaginal fistula may be the result of faulty surgical technique or may occasionally be caused by conditions beyond the control of the most competent surgeon.

When vesicovaginal fistula occurs following complete hysterectomy, it is usually the result of trauma at the time of operation or secondary necrosis and sloughing of tissue about the vaginal vault and base of the

bladder. Postoperative tissue destruction in this area may be caused by infection and/or trophic disturbances from lack of adequate blood supply.

Vesicovaginal fistulas following complete hysterectomy are usually located in the vaginal vault and are invariably difficult to close. Technical difficulties of such operations include:

1. Inaccessibility of the fistulas on account of their location.
2. Fixation of the structures about the vaginal vault and fistulas which result from healing in the presence of infection, tissue necrosis and irritation caused by constant leakage of urine.

Before attempting the closure of such a fistula it is essential to allow sufficient time for complete healing of the tissues about the fistula. When the operation is done, the structures should be as clean and free from infection and induration as possible—this usually requires from three to six months. Healing can frequently be promoted by vaginal douches and local treatments with mild antiseptics. Furthermore operation should not be done until the extent and exact location of the fistula is determined by careful vaginal and cystoscopic examinations. By this precaution ureteral injury at the time of operation may be avoided.

Finally it is important for the operator to determine the most suitable position of the patient for exposure of the fistula at the time of operation and to choose an operative technique best suited for the type of fistula to be closed. Although such fistulas can usually be closed through the vagina, some operators prefer the transvesical route. It is admitted that the latter approach may be preferable in some cases. However, it is not the purpose of this report to discuss the advantages of the two methods of approach but rather to describe a surgical technique whereby two patients with large fistulas were cured by the vaginal route.

In some cases, the classical Sims' position offers the best means of exposing the fistulas. In others satisfactory exposure can be attained in the lithotomy position. Perineotomy, or the Schuchardt incision described by Ward, is useful in nulliparous women and in those in whom the caliber of the vagina is small or is constricted by scar tissue. The lithotomy position was used for the two cases to be reported. As both patients were multiparous women, vaginal incisions were unnecessary.

Numerous surgical techniques have been described for the closure of vaginal fistulas. In general these techniques fall into two classes.

Statistics show that the classical Sims' technique is attended by the highest incidence of success. By this technique the margins of the fistulas are denuded and closed with silver wire sutures. This technique is admirably suited for fistulas which occur on more or less flat surfaces. However, fistulas, in the vaginal vault, are frequently located in a distinct angle between the anterior and posterior vaginal walls. Under such conditions, the Sims' technique is difficult to apply as it is almost impossible to bring the denuded surfaces into exact apposition. If this cannot be accomplished satisfactorily, wound healing cannot be assured.

All other techniques fall into a group in which closure of the fistulas is accomplished by free dissection of the vaginal wall, excision of scar

tissue, mobilization of the bladder, closure of the opening in the bladder wall, and careful closure of the vaginal wall in one or more layers.

In closing fistulas with such techniques, an effort is frequently made to displace the closed defect in the bladder wall by sutures so placed that it does not lie directly beneath the line of suture in the vaginal wall. By this means more certain healing is assured.

In 1918 Rawls described his so-called "fascia lapping" technique for the cure of cystocele. Later he recommended adaptation of the same procedure for the cure of vesicovaginal fistula. This operation which requires careful, painstaking dissection of the anterior vaginal wall was subsequently modified and simplified by Bissell. In the past year Grad described the Bissell technique and reported a series of 100 cases of cystocele operated upon by this method.

The Bissell modification of the Rawls technique for the cure of cystocele was utilized and adapted for the closure of the two fistulas which I wish to report.

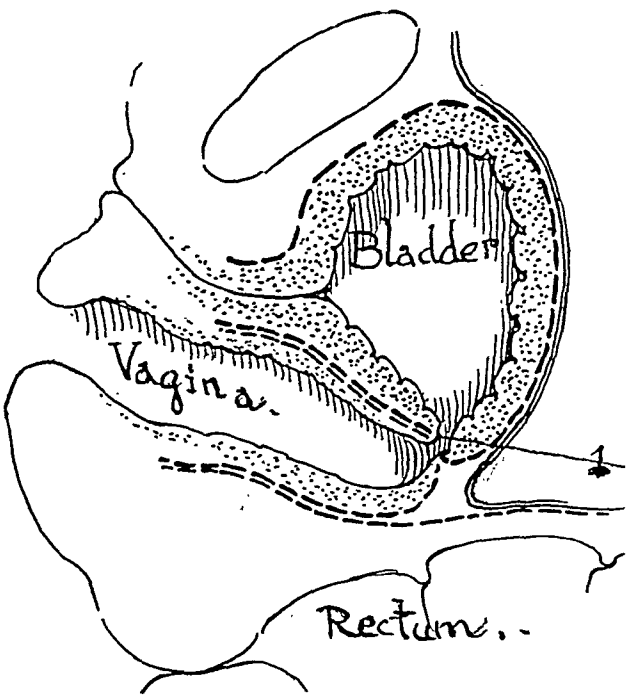


Fig. 1.

TECHNIQUE

Figs. 1 to 6 demonstrate the various steps in the operative procedure which was used to cure large postoperative vesicovaginal fistulas in the two patients whose histories are recorded with this report.

Fig. 1 is a diagram showing the anatomic relationship of the structures about a vesicovaginal fistula which occurs following complete abdominal hysterectomy. It will be noted that the muscular walls of the bladder, and the rectum, and the musculofascial wall of the vagina are completely surrounded by layers of endopelvic fascia indicated by the dotted lines. In opening the anterior or posterior vaginal walls, by midline incisions, experience has shown that free, avascular spaces between the endopelvic fascial coverings of the bladder or rectal musculature and that surrounding the musculofascial walls of the vagina can readily be entered. Dissections are always carried out in these spaces.

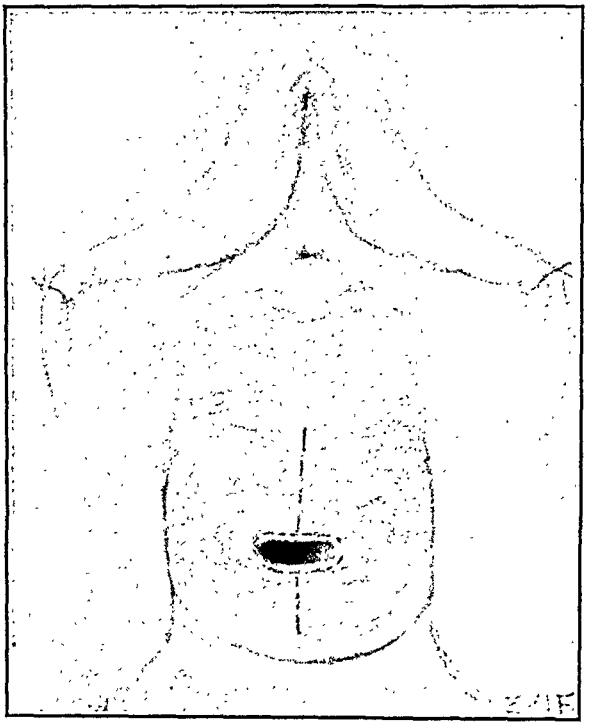


Fig. 2.

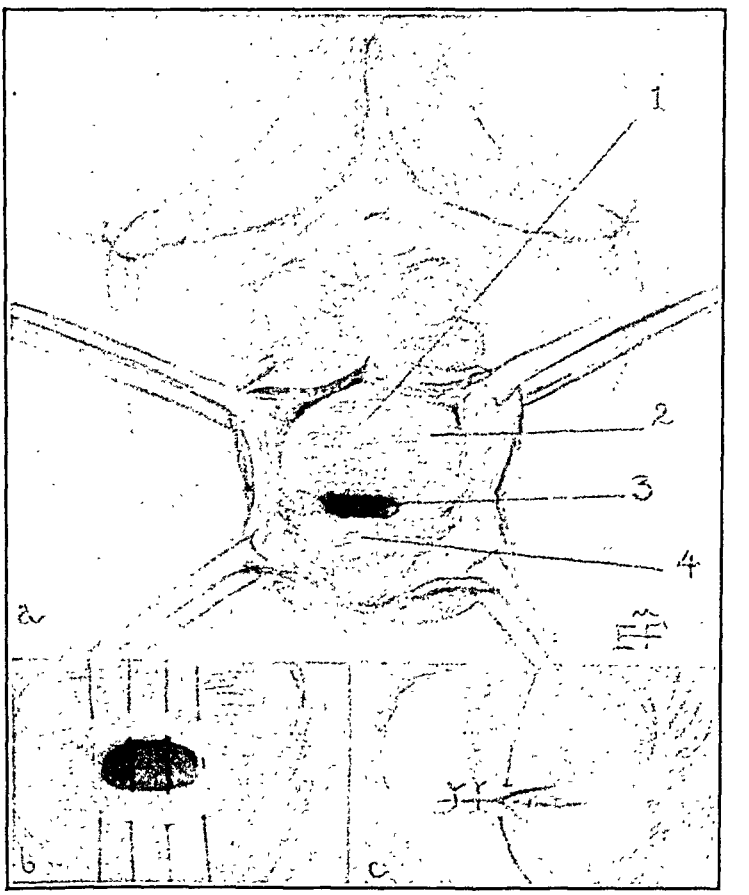


Fig. 3.

Fig. 2 shows the fistula and the dotted lines show the location of the original midline incisions used to open the anterior and posterior vaginal walls. After the proper planes of cleavage have been entered the incisions are continued around the fistula detaching the vaginal walls from its margin.

By blunt dissection the vaginal walls are then freely separated from the rectum, the bladder and the margins of the fistula, as shown in Fig. 3, *a*. In this diagram the margins of the vaginal walls are retracted to show the opening in the bladder, Fig. 3, *a-3;* the wall of the bladder, Fig. 3, *a-1,* and the wall of the rectum Fig. 3, *a-4.*

After all scar tissue has been excised from the margins of the fistula, the opening in the muscular wall of the bladder is closed with interrupted chromic catgut No. 1 sutures placed as shown in Fig. 3, *b* and re-enforced with a second infolding layer as shown in Fig. 3, *c.*

If dissection has been carried out in the proper planes of cleavage, as described above, the endopelvic fascial coverings of the bladder and rectal musculature, Fig. 4, *1* and Fig. 4, *3,* can readily be identified as smooth glistening tissue intimately covering and attached to the muscular walls of the exposed surfaces of these structures.

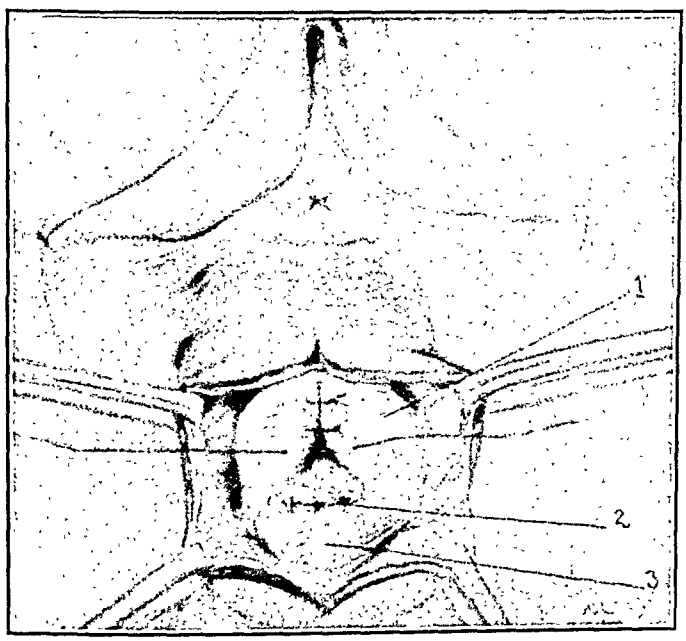


Fig. 4.

As a result of birth injury, the endopelvic fascial coverings of the bladder and rectum are frequently injured in the midline, and their torn margins are retracted laterally in both directions. Therefore, it may be necessary to pick up the margins of this layer of fascia in the sulci between the retracted vaginal walls and exposed surfaces of the bladder and rectum. Davies has recently emphasized the importance of utilizing this layer of fascia for the cure of cystocele.

When the margins of this fascial layer have been identified they are brought into apposition in the midline by interrupted sutures of chromic catgut No. 1, Fig. 4, thereby completely covering the aperture in the bladder wall which has already been closed as described above.

The vaginal walls are then utilized to complete the closure exactly as in the Bissell modification of the Rawls operation for cystocele. The vaginal mucous membrane is denuded from the right flap of vaginal wall Fig. 5, *1,* and the denuded wall is then drawn well beneath the left flap by interrupted mattress sutures of chromic catgut No. 2, as shown in Fig. 5.

The left flap is then fixed over the denuded area on the right flap by interrupted chromic catgut No. 2 sutures, as shown in Fig. 6.

By this procedure therefore the fistulous opening in the bladder is closed with two layers of sutures in the bladder musculature, and the closure is then re-enforced by superimposing the repaired endopelvic fascia and two layers of vaginal wall.

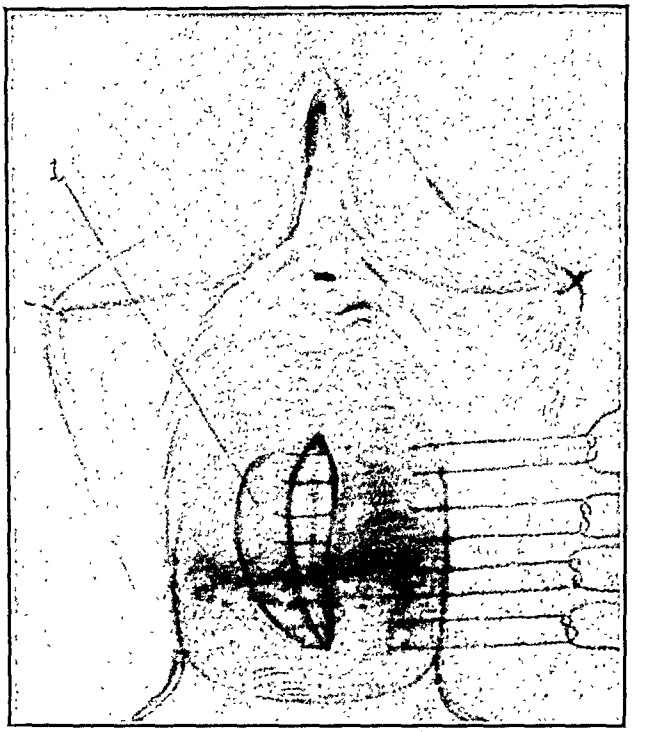


Fig. 5.

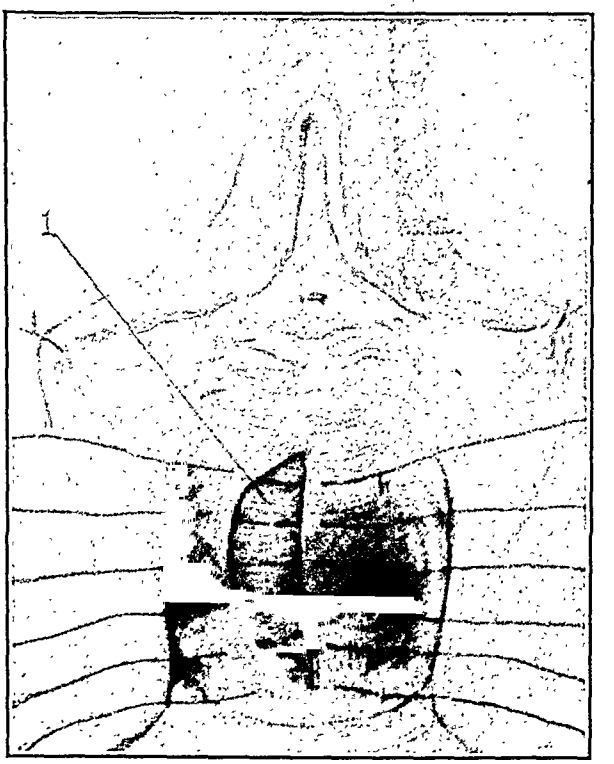


Fig. 6.

The history of the two cases which I wish to report is as follows:

CASE 1.—Mrs. L. M. (No. 56982), aged 39 years, was admitted to the Woman's Hospital on April 25, 1934, complaining of pelvic pain, leucorrhea, and menorrhagia. She had been married fourteen years, had had two pregnancies and spontaneous deliveries. The first labor lasted thirty-six hours. The medical and surgical histories were essentially negative. The blood pressure, urine and blood examinations were all negative.

Pelvic examination revealed a second degree laceration of the pelvic floor, a small rectocele, a small cystocele, a deep stellate laceration of the cervix extending to the vaginal wall on all sides associated with erosion, marked chronic infection and hypertrophy of the cervix. The uterus showed a mass of fibroids the size of a sixteen weeks' pregnancy. The tubes and ovaries were normal. At operation at the Woman's Hospital on April 26, 1934, a complete hysterectomy was done and the appendix, which showed chronic inflammation, was removed. When the uterus was excised from the vaginal vault, it was noted that the vaginal wall, when detached from the cervix, was edematous, sclerotic, and unusually thickened.

The vaginal vault was closed with interrupted sutures of chromic catgut and the detached fascial supports of the uterus were fixed to the vaginal vault. In doing the hysterectomy, no unusual difficulty was encountered in detaching the bladder from the uterus and vagina and so far as was known there was no suspicion of injury to the bladder during the course of the operation.

The highest postoperative temperature was 100.2° F. by rectum. The temperature did not exceed 99.6° F. from the second until the sixteenth day when the patient was discharged from the hospital. The patient was catheterized four times after operation and from then on emptied the bladder spontaneously. On the eleventh postoperative day she passed urine by vagina and was partially incontinent from then until she was discharged. Examination showed an extensive grayish yellow slough in the vaginal vault. This slough gradually separated leaving a vesicovaginal fistula about 2 cm. in diameter exactly in the midline in the vault of the vagina. On account of the relaxation of the vaginal walls, the opening into the bladder could be easily visualized. Healing and shrinking of the tissues about the vaginal vault was so slow that operation to close the fistula was postponed until five months after the first operation. The condition was treated with douches and local antiseptics. When the second operation was undertaken, the tissues appeared clean and free of inflammation.

On Oct. 2, 1934, the fistula was closed by the technique just described. The bladder was drained by retention catheter for ten days and the patient was discharged as cured on the sixteenth postoperative day. Her highest postoperative temperature was 100° F. by rectum. The temperature was normal after the third postoperative day. Subsequent examinations showed a satisfactory result with no apparent shortening of the vagina. It is believed that the postoperative fistula was due to delayed tissue necrosis and slough caused by infection and trophic tissue disturbances.

CASE 2.—Mrs. F. B. (No. 65169), American, aged 39, graduate nurse. Father died of cancer. She had been married twice. She had had one pregnancy and forceps delivery of large baby, weight not known, during first marriage. She had repair of birth injuries and post-partum hemorrhage following this delivery. During the second marriage she had four spontaneous deliveries and one forceps delivery; no abortions. Patient gave a history of having had tonsillectomy in 1912, hospital treatment for "peritonitis" 1932, and seven major abdominal operations for the following conditions: 1918 umbilical hernia, 1927 ulcer of stomach and gastroenterostomy, 1929 ovarian cyst, 1931 peritoneal adhesions, 1935 ovarian cyst, January, 1936 exploratory laparotomy, November, 1936 fibroids, complete abdominal hysterectomy. Had retention of urine requiring catheterization for two weeks before last operation. Stated last operation, complete hysterectomy, was very difficult and that she was on operating table for five hours. She stated that the bladder was drained with retention catheter following this operation, that she leaked urine through the vagina from time of this operation, and that she has had complete incontinence of urine, since this last operation. She passes no urine through the urethra and has

been compelled to wear pads constantly for the ten months since operation. From the history of this operation she apparently had an injury to the bladder at the time of operation and an extensive postoperative pelvic cellulitis. During the ten months she passed blood at times and in July, two months before admission to the hospital, had a severe vaginal hemorrhage which required vaginal packing by an ambulance surgeon.

Examination on admission showed a moderately obese, fairly healthy appearing woman. The general physical examination showed nothing remarkable. The blood count, blood Wassermann and blood sedimentation rate were normal. The abdominal wall showed the scars of numerous healed incisions. Some of the abdominal wounds had apparently been infected and, when healed, had left a mass of scar tissue over a large area between the pubic crest and umbilicus. Vaginal examination showed a deep vagina with a constant leaking of urine through an opening in the vault just to the right of the midline. Without anesthesia the fistulous opening could not be easily visualized by vagina.

Vaginal and cystoscopic examinations showed the vesicovaginal fistula to be at least 2 cm. in diameter slightly to the right of the midline and above the trigone of the bladder. No evidence of neoplasm of the vaginal vault or bladder could be found to account for the bleeding which had been profuse on one occasion. Bleeding had probably come from granulation tissue.

The vaginal vault was fixed by dense scar tissue. The tissues about the vault were somewhat thickened and the mucous membrane was quite reddened and excoriated from the constant leakage of urine.

After five days' rest in the hospital, the fistula was closed on Sept. 22, 1937, by the technique just described. The operation was complicated by the difficulty of exposing the area due to a deep vagina and fixation of structures about the vaginal vault. A retention catheter was left in the bladder for eight days. Following the operation the patient had a rather severe reaction with temperature to 105.4° F. by rectum and a moderate bronchitis for several days. On the fifth day she was transfused with 600 c.c. of blood. The temperature was normal after the tenth day, and she was discharged apparently cured after sixteen days. Examination at time of discharge showed no appreciable shortening of the vagina.

The patient was seen in the follow-up clinic on Nov. 24, 1937, two months after operation. The fistula was solidly healed, and the patient was entirely free of bladder symptoms. The vagina measured 10 cm. in depth.

CONCLUSIONS

1. Complete abdominal hysterectomy is accompanied by an incidence of urinary tract injuries and complications which can be reduced if, unless necessary, only the corpus uteri is removed.

2. Postoperative vesicovaginal fistula is one of the less frequent but most distressing complications which may follow complete abdominal hysterectomy.

3. The Bissell modification of the Rawls technique for the cure of cystocele can be effectively adapted for the closure of certain vesicovaginal fistulas.

33 EAST SIXTY-EIGHTH STREET

FETAL AND NEONATAL DISEASE AND DEATH*

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IT IS often difficult for adults to realize that the diseases with which they are afflicted may arise from factors determined before birth, and in some instances even before conception. A battle is still waged between those who believe that heredity is the main factor in determining the pattern of individual existence and those who believe that it is largely limited by environmental states. It is frequently forgotten however that environment antedates birth and that it affects not only the embryo or fetus in utero but also the germ cells before their discharge from the gonads.

Abnormalities leading to defects of development, disease or death, which have their origin in the preconceptional state may be due to transmissible factors present in the genes and predetermined by specific ancestry; they may be caused by noninherited defects of germ plasm due to initial imperfections in the germ cell or they may be due to unpropitious environmental states which modify the original character of the ovum or spermatozoon.

In the first group fall such known transmissible pathologic conditions as hemophilia, polydactylism, albinism, etc. In addition to inheritance of body build and facial characteristics it is most reasonable to believe that the structure of organs and their potential capacity for growth and function are in part at least also determined by inheritance. Pearl has conclusively shown that the best way to live to old age is to be born of parents and grandparents who were octogenarians.

Environmental states affecting the germ cells include the entire physiologic mechanism of the individual. Abnormal hormonal states may interfere with normal maturation of the ovum or may inhibit fertilization after expulsion from the ovary. Extraneous influences, of which the most easily demonstrable are the effects of radium and roentgen rays may have a definitely injurious effect on germ cells.

After fertilization has occurred both the inherent qualities present in the zygote and the environment to which it is subjected determine both the normality of implantation and the embryonic and fetal development. Many embryos and fetuses succumb to unknown and nondemonstrable lethal factors. These ultimately may be shown to be due to inadequate germ plasm or be proved to be associated with vitamin, hormone, or other chemical influences during intrauterine environment.

The most important conditions which are known causes of death in fetal life are environmental. Malformations are an important cause of

*Read at a meeting of the Brooklyn Gynecological Society, Brooklyn, New York, February 4, 1938.

death in the embryonic and in the immediate postnatal period. If an abnormality is not of sufficient grade to cause death in the first few weeks of development, it is usually compatible with intrauterine fetal life and death is infrequent up to the time the fetus is born. Maternal disease of any type may affect the fetus either by interfering with normal nutrition or by a direct transference of toxic or infectious substances from the maternal to the fetal blood stream.

Abnormalities of the accessory fetal structures, amnion, placenta and cord, are largely environmental in origin. Premature separation of the placenta, which is often very injurious to the fetus, is frequently associated with some type of toxemia, and is definitely environmental. The cause of placenta previa is not definitely known, and it is possible that an abnormality either of the uterus or the ovum may be responsible. The most serious condition which affects the umbilical cord is its prolapse through the introitus. This rarely occurs if the membranes do not rupture until the presenting part is well engaged.

The period during which the fetus traverses the birth canal forms the most perilous interval of its entire intranatal or postnatal existence. This hazard is greatly increased if labor occurs before the fetus is mature; approximately ten times as many of the fetuses who are delivered prematurely die during delivery as of those who are delivered at term. In addition to prematurity the greatest birth hazards are those conditions which interfere with placental circulation, which cause trauma to the central nervous system or to the abdominal viscera, and which favor the ascent of infectious material from the lower genital tract into the amniotic sac or uterus. In the first group the fetuses die of anoxemia, in the second, of direct injury to the nerve centers in the brain or from visceral hemorrhage, in the third of acute infections which especially affect the lungs.

If the fetus survives the process of delivery it must still adjust itself to the rigors of an extrauterine existence; it must maintain its own body temperature, digest its own food, inhale its own oxygen, and eliminate its own waste products. It is suddenly exposed to the bacteria of a contaminated world. Fortunately in civilized countries the young infant is greatly protected from contact with harmful bacteria so that in the first few weeks of life the main causes of morbidity or mortality are the persistent effects of conditions affecting the fetus during the intrauterine period or during the establishment of extrauterine life. In later infancy bacterial infections cause a large proportion of the total deaths.

Any of the antenatal, intranatal, or postnatal factors which produce disorders of the fetus or infant may be carried into later infant, child, and even adult life to produce a handicapped existence or shortened life expectancy.

In the United States there has been a progressive reduction in the total death rate and a continual diminution in the infant mortality rate for many years. A close analysis of the latter, however, reveals that there has been little if any reduction in the neonatal death rate and practically none in the fetal death rate. In the United States mortality statistics for

the first year of life show a gradual decrease since 1915 (100 deaths per 1,000 live births in 1915, 56 per 1,000 births in 1935); the mortality subsequent to the first month of life shows a more marked decline (58 per 1,000 live births in 1915, 25 per 1,000 live births in 1935), but the mortality rate for the first day is almost a straight line from 1915 to 1935 (16 per 1,000 live births throughout the entire period), and the death rate during the first month shows only a very slight decrease (44 per 1,000 live births in 1915, 34 per 1,000 live births in 1935). The number of stillbirths has remained practically constant since figures on this subject have been collected by the census bureau (40 per 1,000 live births in 1922, 38 per 1,000 live births in 1934). While certain factors such as the more complete reporting, especially of premature births, may obscure some saving of life during this early period, the fact remains that only slight progress in a general reduction of the number of stillbirths or early infant deaths has been made.

It is difficult to compare statistics from any two countries or from any two institutions within the same country because of the variation in classification and of the age limits included. It would be of great help in evaluating methods used in treatment of the complications of pregnancy and labor if fetal and neonatal mortality could be accurately compared in different clinics. The only way to accomplish this is to have a uniform system adopted throughout the country.

The method found most valuable at the Chicago Lying-in Hospital is to use three criteria (menstrual age, fetal weight, and length) in determining the probable age of the fetus (Table I). All fetuses and infants

TABLE I. CRITERIA FOR ESTABLISHING AGE OF FETUS AND NEWBORN INFANT AT THE CHICAGO LYING-IN HOSPITAL*

I. Abortion	
	1. Less than 400 gm. in weight
	2. Less than 28 cm. in length
	3. Less than 22 weeks (missed abortions are excluded)
II. Premature	
A. Previable	
	1. From 400 to 999 gm. in weight
	2. From 28 cm. to 35 cm. in length
	3. From 22nd to the end of the 28th week
B. Viable	
	1. From 1000 to 2499 gm. in weight
	2. From 35.1 cm. to 47 cm. in length
	3. From 29th to the end of the 37th week
III. Term	
	1. From 2500 to 4499 gm. in weight
	2. From 47.1 cm. to 54 cm. in length
	3. From 38th to the end of the 42nd week
IV. Postmature	
	1. More than 4500 gm. in weight
	2. More than 54 cm. in length
	3. More than 42 weeks

*The infant is placed in the group in which two of the three criteria fall.

for which a stillbirth or death certificate is required by law are included in mortality reports. This includes many fetuses which have not yet

reached the period of viability and which cannot be expected to survive. The only justification for the use of "corrected mortality" figures is in those instances where an evaluation of a certain procedure makes it necessary to eliminate those cases in which the factor being investigated could not have played a contributing part. Citing "corrected mortality rates" as a hospital's actual mortality is never justified.

In the Chicago Lying-in Hospital from May 25, 1931, to Jan. 1, 1938, there were 17,728 deliveries, with 371 neonatal deaths and 402 stillbirths. The incidence of the various methods of delivery and the number of deaths occurring in each type are shown in Tables II and III.

TABLE II. INCIDENCE OF VARIOUS TYPES OF DELIVERY

	TOTAL NUMBER OF DELIVERIES	INCIDENCE PER CENT
Cephalic, natural	10,877	61.9
Cephalic, low forceps	3,995	22.5
Cephalic, midforceps	835	4.7
Breech	708	4.0
Cesarean section	1,041	5.8
Version and extraction	162	0.9
Miscellaneous	110	0.6

TABLE III. TYPE OF DELIVERY IN RELATION TO FETAL AND NEONATAL DEATHS

	TOTAL DELIVERIES	STILL-BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	PER CENT
Cephalic, natural	10,877	170	174	344	3.0
Cephalic, low forceps	3,995	22	35	57	1.4
Cephalic, midforceps	835	22	20	42	5.0
Breech	708	61	56	117	16.5
Cesarean section	1,041	31	62	93	8.9
Version and extraction	162	35	23	58	34.5
Miscellaneous (Includes 59 craniotomies)	110	61	1	62	56.3

It is important to know the incidence of the various fetal age groups and the mortality rates of the different groups. Table IV shows that our total rate per thousand live born infants is 44, with a stillbirth rate of 23 and a neonatal death rate of 21. If one considers only the previable infants and fetuses, the corresponding rates are 988, 462, and 526, respectively. The corresponding rates for the viable prematures are 346, 165, and 181, respectively, and for term infants, they are 18, 10,

TABLE IV. MORTALITY RATES IN RELATION TO FETAL AGE AT TIME OF DELIVERY

	TOTAL BIRTHS	TOTAL NEONATAL MORTALITY	NEONATAL MORTALITY PER 1,000 BIRTHS	TOTAL STILL-BIRTHS	STILL-BIRTH MORTALITY PER 1,000 BIRTHS	TOTAL MORTALITY PER 1,000 BIRTHS
Term	16,529	133	8	189	10	18
Premature	1,043	189	181	170	165	346
Previable	93	49	526	43	462	988
Undetermined	63	---	---	---	---	---
Total	17,728	371	20	402	22	43